4-(2,6-difluoro-phenoxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(4-ethanesulfonyl-phenoxy)-benzene-1,2-diamine obtained in Example 426, the title compound was obtained by the same process as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 6.23 (1H, brs), 7.08 (1H, brs), 7.15-7.22 (4H, m), 7.28-7.38 (1H, m), 7.51 (1H, t, J = 5.9 Hz), 7.87 (2H, d, J = 9.0 Hz), 8.00 (1H, t, J = 7.4 Hz), 8.41 (1H, d, J = 7.4 Hz), 8.76 (1H, brs).

ESI-MS (m/e): 508 (M+H).

Example 428

4-(2-difluoromethyl-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2-difluoromethyl-phenol and 6-ethanesulfonyl-pyridin-3-ol were used successively and the title compound was obtained as a colourless solid by the same process as in Example 274, a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.50 (1H, s), 7.15 (1H, d, J = 7.4 Hz), 7.22 (1H, t, J = 55.5 Hz), 7.34 (1H, t, J = 7.4 Hz), 7.49-7.62 (4H, m), 7.74 (1H, d, J = 7.4 Hz), 7.98 (1H, t, J = 7.4 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.37 (1H, d, J = 7.4 Hz), 8.49 (1H, d, J = 2.3 Hz), 8.74-8.77 (1H, m).

ESI-MS (m/e): 523 (M+H).

Example 429

4-(2-difluoromethyl-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(2-difluoromethyl-phenoxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene -1,2-diamine obtained in Example 428, the title compound was obtained as yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.25 (3H, t, J = 7.8 Hz), 3.40 (2H, q, J = 7.8 Hz), 6.54 (1H, s), 7.17 (1H, d, J = 7.4 Hz), 7.21 (1H, t, J = 55.8 Hz), 7.36 (1H, t, J = 7.4 Hz), 7.50-7.65 (2H, m), 7.75 (1H, d, J = 7.4 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.72 (1H, s), 8.79 (1H, s), 9.54 (1H, s).

ESI-MS (m/e): 524 (M+H).

Example 430

4-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

2-difluoromethoxy-pyridin-3-ol and 4-ethansulphonyl-phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

1H-NMR(CD3OD) δ : 1.25 (3H, t, J = 7.3 Hz), 3.40 (2H, q, J = 7.3 Hz), 6.60 (1H, d, J = 2.0 Hz), 7.27-7.30 (2H, m), 7.57-7.61 (2H, m), 7.64 (1H, t, J = 72.1 Hz), 7.73 (1H, dd, J = 7.8, 1.6 Hz), 8.05-8.08 (2H, m), 8.10 (1H, dd, J = 4.9, 1.6 Hz), 8.37 (1H, d, J = 8.2 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.81 (1H, d, J = 4.9 Hz).
ESI-MS (m/e): 540 (M+H).

Example 431

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole

Using

3-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-5-(4-ethanesulfonyl-phenoxy)-benzene-1,2-diamine obtained in Example 274 (Step 1), the title compound was obtained as a pale yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 3.65 (3H, s), 6.38 (1H, t, J = 7.2 Hz), 6.44 (1H, s), 7.07 (1H, s), 7.15-7.22 (2H, m), 7.40 (1H, d, J = 7.0 Hz), 7.57 (1H, dd, J = 7.0, 1.8 Hz), 7.84-7.90 (2H, m), 8.70 (1H, s), 8.76 (1H, s), 9.52 (1H, s).
ESI-MS (m/e): 504 (M+H).

Example 432

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

1-methyl-2-oxo-1,2-dihydro-pyridin-3-ol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.
1H-NMR(CD3OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.65 (5H, s), 6.36 (1H, t, J = 6.7 Hz), 6.46 (1H, s), 7.13 (1H, s), 7.38-7.60 (4H, m), 7.95-8.08 (2H, m), 8.35 (1H, s), 8.49 (1H, s), 8.73 (1H, s).
ESI-MS (m/e): 504 (M+H).

Example 433

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 432, the title compound was obtained as a pale yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.
1H-NMR (DMSO-d6) δ : 1.13 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.50 (3H, s), 6.24 (1H,

t, J = 6-8 Hz), 6.46 (1H, s), 7.05 (1H, brs), 7.32-7.40 (1H, m), 7.58 (1H, dd, J = 8.8, 2.5 Hz), 7.74 (1H, dd, J = 6.8, 2.0 Hz), 8.01 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 2.5 Hz), 8.79 (1H, d, J = 2.2 Hz), 8.82 (1H, dd, J = 2.5, 1.5 Hz), 9.47 (1H, d, J = 1.4 Hz).
ESI-MS (m/e): 505 (M+H).

Example 434

4-(2-cyano-pyridin-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H- benzimidazole

Step 1

Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-nitro -3-(1-oxy-pyridin-3-yloxy)- phenylamine

Using 1-oxy-pyridin-3-ol and 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained by the same process as in Example 67 (Step 1) and (Step 2), a process based on these or a combination of these with a normal procedure and this.

Step 2

Synthesis of 5-(4-methanesulphonyl-phenoxy)-2- nitro-3-(2-cyano-pyridin-3-yloxy)-phenylamine

Using 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(1-oxy-pyridin-3-yloxy)-phenylamine, the title compound was obtained by the same process as in Example 218 (Step 2), a process based on this or a combination of these with a normal procedure.

Step 3

Production of 4-(2-cyano-pyridin-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2 -pyridin- 2-yl -1H-benzimidazole

Using 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(2-cyano-pyridin-3-yloxy)-phenylamine, the title compound was obtained by the same process as in Example 196 (Step 5) and 204 (Step 1), a process based on these or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 3.23 (3H, s), 7.07 (1H, brs), 7.44 (1H, brs), 7.56-7.69 (4H, m), 8.02 (1H, t, J = 7.8 Hz), 8.09 (1H, d, J = 8.6 Hz), 8.29 (1H, d, J = 7.8 Hz), 8.46-8.48 (1H, m), 8.55-8.57 (1H, m), 8.78-8.80 (1H, m).
ESI-MS (m/e): 485 (M+H).

Example 435

4-(2-cyano-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H- benzimidazole

Using 4-ethanesulphonyl-phenol, the title compound was obtained by the same process as in Example 434, a process based on this or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 1.25 (3H, t, J = 7.3 Hz), 3.22 (2H, q, J = 7.3 Hz), 6.94 (1H, brs), 7.27 (2H, d, J = 8.6 Hz), 7.33 (1H, brs), 7.49 (2H, d, J = 8.6 Hz), 7.59-7.62 (1H, m), 7.91-7.98 (3H, m), 8.24 (1H, d, J = 8.6 Hz), 8.45 (1H, d, J = 5.1 Hz), 8.74 (1H, d, J = 5.5 Hz)

ESI-MS (m/e): 498 (M+H).

Example 436

4-benzyloxy-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Benzyl alcohol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

1H-NMR(CD3OD) δ : 1.24 (3H, t, J = 7.6 Hz), 3.45 (2H, q, J = 7.6 Hz), 5.41 (2H, s), 7.02-7.05 (1H, m), 7.15-7.17 (1H, m), 7.39-7.45 (3H, m), 7.53-7.59 (4H, m), 8.07 (1H, d, J = 8.6 Hz), 8.11-8.14 (1H, m), 8.39 (1H, d, J = 7.0 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.87-8.90 (1H, m).

ESI-MS (m/e): 487 (M+H).

Example 437

4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-benzyloxy-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 436, the title compound was obtained by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.27 (3H, t, J = 7.4 Hz), 3.42 (2H, q, J = 7.4 Hz), 5.38 (2H, s), 6.80 (1H, d, J = 2.0 Hz), 7.06 (1H, d, J = 2.0 Hz), 7.36-7.42 (3H, m), 7.49 (1H, dd, J = 8.8, 2.9 Hz), 7.54 (2H, d, J = 6.7 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.7 Hz), 8.78-8.80 (1H, m), 9.54-9.56 (1H, m).

ESI-MS (m/e): 488 (M+H).

Example 438

4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Step 1

Synthesis of 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy) -2-pyridin-2-yl-1H- benzimidazole

Using 4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 436, the title compound was obtained by the same process as in Example 251 (Step 1), by a process based on this or a combination of these with a normal procedure.

Step 2

Production of 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin -3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole and 2,3-difluoro benzonitrile, the title compound was obtained by the same process as in Example 251 (Step 2), by a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.61 (1H, d, J = 2.0 Hz), 7.28 (1H, d, J = 2.0 Hz), 7.36-7.42 (1H, m), 7.48-7.54 (1H, m), 7.58-7.63 (2H, m), 7.65-7.69 (1H, m), 8.07 (2H, d, J = 8.2 Hz), 8.38 (1H, d, J = 7.8 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.82 (1H, d, J = 4.7 Hz).
ESI-MS (m/e): 516 (M+H).

Example 439

4-(6-cyano-pyridin-2-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H- benzimidazole

Using 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 438 (Step 1) and 2-chloro-3-cyanopyridine, the title compound was obtained by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.42 (2H, q, J = 7.4 Hz), 7.21 (1H, d, J = 2.0 Hz), 7.30 (1H, dd, J = 7.4, 5.1 Hz), 7.48 (1H, d, J = 2.0 Hz), 7.58 (1H, dd, J = 5.1, 7.8 Hz), 7.71 (1H, dd, J = 8.8, 2.9 Hz), 8.00-8.05 (1H, m), 8.11 (1H, d, J = 8.6 Hz), 8.26-8.33 (3H, m), 8.60 (1H, d, J = 2.7 Hz), 8.78 (1H, d, J = 5.1 Hz).
ESI-MS (m/e): 499 (M+H).

Example 440

4-(2-cyano-3-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 2,6-difluoro benzonitrile, the title compound was obtained by the same process as in Example 439, a process based on this or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 1,26 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.91 (1H, d, J = 8.6 Hz), 7.04 (1H, d, J = 1.8 Hz), 7.13 (1H, t, J = 8.6H.z), 7.44 (1H, d, J = 1.8 Hz), 7.55-7.64 (2H, m), 7.67 (1H, dd, J = 8.6, 3.2 Hz), 8.00-8.06 (1H, m). 8.10 (1H, d, J = 8.6 Hz), 8.33 (1H, d, J = 7.8 Hz), 8.57 (1H, d, J = 2.3 Hz), 8.78-8.81 (1H, m).
ESI-MS (m/e): 516 (M+H).

Example 441

4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 438, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.53 (1H, brs), 7.26 (1H, brs), 7.42-7.53 (2H, m), 7.57-7.62 (2H, m), 7.68 (1H, dd, J = 8.2, 3.9 Hz), 8.07 (1H, d, J = 8.6

Hz), 8.11-8.16 (1H, m), 8.41 (1H, d, J = 8.2 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.88 (1H, d, J = 3.9 Hz)
ESI-MS (m/e): 534 (M+H).

Example 442

4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 437, the title compound was obtained by the same process as in Example 438, a process based on this or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.57 (1H, brs), 7.23 (1H, brs), 7.46-7.51 (1H, m), 7.57-7.61 (1H, m), 7.64-7.71 (2H, m), 8.06 (1H, d, J = 9.0 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.71 (1H, d, J = 2.3 Hz), 8.78 (1H, s), 9.48 (1H, s).
ESI-MS (m/e): 517 (M+H).

Example 443

4-(2-cyano-5-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 2,4-difluoro-benzonitrile and 4-hydroxy-6-(6-ethanesulfonyl- pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 442, the title compound was obtained by same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 1.20 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.88 (1H, d, J = 10.2 Hz), 6.98 (1H, d, J = 2.0 Hz), 7.05-7.11 (1H, m), 7.39-7.44 (1H, m), 7.68 (1H, dd, J = 3.1, 8.0 Hz), 7.89 (1H, dd, J = 8.8, 6, IHz), 8.08-8.12 (1H, m), 8.57-8.60 (1H, m), 8.71 (1H, d, J = 2.3 Hz), 8.77-8.79 (1H, m), 9.46-9.48 (1H, m).
ESI-MS (m/e): 517 (M+H).

Example 444

4-(2-cyano-4-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 2,5-difluoro benzonitrile, the title compound was obtained by the same process as in Example 443, by a process based on this or a combination of these with a normal procedure.
1H-NMR(CD3OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.81 (1H, d, J = 2.3 Hz), 7.22 (1H, dd, J = 4.6, 9.0 Hz), 7.35 (1H, d, J = 2-3 Hz), 7.45 (1H, ddd, J = 8.6, 4.6, 7.4 Hz), 7.63-7.69 (2H, m), 7-72-7.75 (1H, m), 8.09 (1H, d, J = 8.6 Hz), 8.55 (1H, d, J = 3.1 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79 (1H, dd, J = 2.0, 3.1 Hz), 9.49 (1H, d, J = 2.0 Hz).
ESI-MS (m/e): 517 (M+H).

Example 445

4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2- pyrazin-2-yl -1H-benzimidazole obtained in Example 442, the title compound was obtained by same process as in Example 43, by a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.39 (1H, s), 7.21 (1H, s), 7.42-7.51 (2H, m), 7.55 (1H, dd, J = 8.6, 2.7 Hz), 7.64 (1H, d, J = 7.4 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.7 Hz), 8.75-8.78 (1H, m), 8.82-8.84 (1H, m), 9.54 (1H, brs).

ESI-MS (m/e): 535 (M+H).

Example 446

4-(6-cyano-pyridin-2-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H- benzimidazole

Using 2-chloro-3-cyanopyridine, the title compound was obtained by the same process as in Example 443, a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 7.14 (1H, d, J = 2.0 Hz), 7.30 (1H, dd, J = 7.4, 5.1 Hz), 7.45 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 9.0, 2.7 Hz), 8.10 (1H, d, J = 9.0 Hz), .8.27-8.33 (2H, m), 8.59 (1H, d, J = 2.7 Hz), 8.70-8.72 (1H, m), 8.76-8.79 (1H, m), 9.41-9.43 (1H, 1).

ESI-MS (m/e): 500 (M+H).

Example 447

4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained as a pale yellow solid by the same process as in Example 438, a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 3.23 (3H, s), 6.50 (1H, s), 7.22/(1H, s), 7.45-7.62 (3H, m), 7.62-7.78 (2H, m), 7.95-8.05 (1H, m), 8.08 (1H, d, J = 8.8 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.49 (1H, s), 8.77 (1H, s).

ESI-MS (m/e): 502 (M+H).

Example 448

4-(2-fluoro-6-methanesulphonyl-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 2,3-difluoro-methanesulphonyl benzene and 4-hydroxy-6-(6-methanesulphonyl -pyridin -3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 447, the title compound was

obtained by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 3.21 (3H, s), 3.46 (3H, s), 6.54 (1H, d, J = 2.0 Hz), 7.27 (1H, d, J = 2.0 Hz), 7.54-7.67 (3H, m), 7.70-7.74 (1H, m), 7.93 (1H, d, J = 7.8 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.11 (1H, ddd, J = 7.8, 8,6,2.7 Hz), 8.40 (1H, d, J = 7.8 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.86 (1H, d, J = 5.1 Hz).

ESI-MS (m/e): 555 (M+H).

Example 449

4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy) -2-pyridin-2 -yl-1H-benzimidazole obtained in Example 447, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 3.22 (3H, s), 6.53 (1H, d, J = 1.6 Hz), 7.25 (1H, d, J = 1.6 Hz), 7.42-7.53 (2H, m), 7.57 (1H, dd, J = 8.6, 2.7 Hz), 7.61 (1H, d, J = 7.4 Hz), 7.68 (1H, dd, J = 7.6, 14.3 Hz), 8.06 (1H, d, J = 9.0 Hz), 8.10-8.16 (1H, m), 8.41 (1H, d, J = 8.2 Hz), 8.47 (1H, d, J = 2.7 Hz), 8.8.7 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 520 (M+H).

Example 450

4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained by the same process as in Example 442, a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 3.23 (3H, s), 6.57 (1H, brs), 7.23 (1H, brs), 7.49 (1H, td, J = 8.0, 4.6 Hz), 7.59 (1H, dd, J = 9.0, 3.2 Hz), 7.65-7.71 (2H, m), 8.07 (1H, d, J = 9.0 Hz), 8.50 (1H, d, J = 2.3 Hz), 8.71 (1H, d, J = 2.3 Hz), 8.78 (1H, brs), 9.48 (1H, brs).

ESI-MS (m/e): 503 (M+H).

Example 451

4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained as pale-brown solid by the same process as in Example 288, a process based on this or a combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.31 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.03 (1H, d, J = 8.0 Hz),

7.08 (1H, ddd, J = 7.4, 4.7, 1.0 Hz), 7.35 (1H, d, J = 2.2 Hz), 7.38-7.44 (2H, m), 7.52 (1H, td, J = 7.8, 2.0 Hz), 7.64 (1H, d, J = 2.1Hzl), 7.88 (1H, td, J = 7.8, 1.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.38 (1H, d, J = 7.8 Hz), 8.45 (1H, dd, J = 4.9, 1.0 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.64 (1H, d, J = 4.9 Hz).
ESI-MS (m/e): 490 (M+H).

Example 452

4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(pyridin-2-yl sulphanyl)-5-(6-ethanesulfonyl-pyridin -3-yloxy)-benzene-1,2- diamine obtained in Example 451, the title compound was obtained as yellow solid by the same method as in-Example 68, a process based on this or a combination of these with a normal procedure.
1H-NMR (CDCl3) □ : 1.32 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.08-7.19 (2H, m), 7.38 (1H, d, J = 2.2 Hz), 7.43 (1H, dd, J = 8.6, 2.8 Hz), 7.57 (1H, td, J = 7.8, 1.8 Hz), 7.66 (1H, d, J = 2.2 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 4.7 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.63 (1H, t, J = 2.0 Hz), 8.69 (1H, d, J = 2.5 Hz), 9.63 (1H, d, J = 1.4 Hz)
ESI-MS (m/e): 491 (M+H).

Example 453

4-(1-methyl-1H-imidazol-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin -2-yl -1H-benzimidazole

Using 1-methyl-1H-imidazole-2-thiol, the title compound was obtained as yellow solid by the same process as in Example 452, a process based on this or a combination of these with a normal procedure.
1H-NMR (CDCl3) □ : 1.33 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 3.94 (3H, s), 6.65-6.69 (1H, m), 6:77 (1H, d, J = 1.4 Hz), 6.87 (1H, d, J = 1.6 Hz), 7.23 (1H, d, J = 2.4 Hz), 7.48 (1H, dd, J = 8.6, 2.8 Hz), 7.72 (1H, d, J = 2.2 Hz), 8.05 (1H, dd, J = 8.6, 0.6 Hz), 8.16 (1H, d, J = 2.6 Hz), 8.54 (1H, dd, J = 2,8,0.6 Hz), 9.42 (1H, d, J = 1.6 Hz).
ESI-MS (m/e): 494 (M+H).

Example 454

4-(4-methoxybenzyl-sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using (4-methoxyphenyl) methanethiol, the title compound was obtained as a brown solid by the same process as in Example 452, a process based on this or a combination of these with a normal procedure.
1H-NMR (CDCl3) □ : 1.32 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.61 and 3.79 (total 3H, each s), 4.05 and 4.40 (total 2H, each s), 6.69 and 6.79 (total 2H, each d, J = 8.6 Hz), 6.88-7.52

(5H, m), 7.98 and 8.01 (total 1H, each d, J = 8.6 Hz), 8.44 and 8.46 (total 1H, each d, J = 2-9 Hz), 8.58-8.65 (1H, m), 8.68 and 8.70 (total 1H, each d, J = 2.5 Hz), 9.58 and 9.74 (d, J = 114 Hz), 10.05 and 10.46 (total 1H, each brs).
ESI-MS (m/e): 534 (M+H).

Example 455

4-(6-cyano-pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy) -2-pyrazin-2-yl -1H-benzimidazole

Using 2-chloro-3-cyanopyridine, the title compound was obtained as a pale yellow solid by the same process as in Example 446, a process based on this or a combination of these with a normal procedure.
1H-NMR (CDCl3) δ : 1.32 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.20 (1H, dd, J = 7.8, 4.9 Hz), 7.41 (1H, d, J = 2.2 Hz), 7.45 (1H, dd, J = 8.8, 2.8 Hz), 7.72 (1H, d, J = 2.2 Hz), 7.93 (1H, dd, J = 7.8, 1.8 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.44 (1H, dd, J = 4.9, 2.0 Hz), 8-54 (1.H, d, J = 2.8 Hz), 8.62 (1H, dd, J = 2.5, 1, 5 Hz), 8.70 (1H, d, J = 2.5 Hz), 9.64 (1H, d, J = 1.5 Hz).
ESI-MS (m/e): 516 (M+H).

Example 456

4-(2-cyano-pyridin-3-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H -benzimidazole

Using 2-cyano-3-fluoropyridine and 4-mercapto-6-(6-ethanesulphonyl -pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 455, the title compound was obtained as pale yellow solid by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.
1H-NMR (DMSO-d6) δ : 1.13 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.22 (1H, s), 7.41 (1H, s), 7,64 (2H, dd, J = 8.6, 2.7 Hz), 7.96-8.04 (2H, m), 8.59-8.66 (2H, m), 8.77-8.83 (2H, m), 9.32 (1H, s).
ESI-MS (m/e): 516 (M+H).

Example 457

4-(pyridin-2-yl sulphanyl)-5-chloro-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl -1H-benzimidazole

Using pyridine-2-thiol, the title compound was obtained as a pale yellow solid by the same procedures as in Example 117 and Example 290, a process based on these or a combination of these with a normal procedure.
1H-NMR (CDCl3) δ : 1.31 (3H, t, J = 7.4 Hz)-, 3.40 (2H, q, J = 7.4 Hz), 7.2 (1H, d, J = 7.5 Hz), 7.05-7.10 (1H, m), 7.31 (1H, dd, J = 8.6, 2.7 Hz), 7.41 (1H, t, J = 6.0 Hz), 7.53 (1H, t, J = 7.4 Hz), 7.75 (1H, s), 7.88 (1H, t, J = 7.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.41 (1H,

d, J = 4.1 Hz), 8.50 (1H, d, J = 2.5 Hz), 8.63 (1H, s).
ESI-MS (m/e): 524,526 (M+H).

Examples 458-1, 458-2

4-(pyridin-2-yl sulphinyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole
and
4-(pyridin-2-yl sulfonyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H- benzimidazole

To methanol 3 ml solution of 4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole 20 mg obtained in Example 451 were added OXONE 50 mg and water 0.5 ml, and the reaction liquor was stirred at room temperature for three hours. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was diluted with ethyl acetate and was washed with water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. Saturated aqueous sodium bicarbonate was added to the obtained fraction and thereafter, it was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

4-(pyridin-2-yl sulphinyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole
1H-NMR (CDCl3) δ : 1.33 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.35 (1H, dd, J = 8.8, 2.7 Hz), 7.37-7.45 (2H, m), 7.55 (1H, d, J = 2.1 Hz), 7.61 (1H, d, J = 2.1 Hz), 7.89 (1H, t, J = 7.8 Hz), 7.96 (1H, t, J = 7.8 Hz), 8.02 (1H, d, J = 8.6 Hz), 8.15 (1H, d, J = 8.2 Hz), 8.37 (1H, d, J = 7.8 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.65 (1H, d, J = 3.7Hz), 8.76 (1H, d, J = 4.5 Hz).
ESI-MS(m/e): 506 (M+H).

4-(pyridin-2-yl sulfonyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzoimidazole
1H-NMR (CDCl3) δ : 1.33 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.37 (1H, dd, J = 8.6, 2.8 Hz), 7.44-7.49 (1H, m), 7.55 (1H, dd, J = 7.4, 4.5 Hz), 7.70 (1H, d, J = 1, 8 Hz), 7.80 (1H, d, J = 2.2 Hz), 7.88-7.94 (1H, m), 7.96-8.02 (1H, m), 8.04 (1H, d, J = 8.6 Hz), 8.26 (1H, d, J = 7.4 Hz), 8.40 (1H, d, J = 8.0 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.73 (1H, d, J = 4.7 Hz), 8.77 (1H, d, J = 4.9 Hz).
ESI-MS (m/e): 522 (M+H).

Example 459

6-(1-acetyl pyrrolidin-2-yl)-5-((2'-fluoro biphenyl-4-yl) oxy)-2-pyridin-2-yl-1H- benzimidazole

Using 2'-fluoro biphenyl-4-ol, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.00-2.60 (7H, m), 3.40-4.00 (2H, m), 5.20-5.65 (1H, m), 7.00-7.70 (11H, m), 7.80-8.00 (1H, m), 8.25-8.45 (1H, m), 8-50-8.70 (1H, 1).

ESI-MS (m/e): 493 (M+H).

Example 460

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H- benzimidazole • monotrifluoroacetic acid salt

Step 1

Synthesis of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde

To N-methyl-2-pilori di Don 1 ml solution of 1-(2-(6-hydroxy-2-pyridin-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 100 mg obtained in Example 121 (Step 11) were added successively cesium carbonate 143 mg, p-fluoro benzaldehyde 0.048 ml, and the reaction liquor was heated with stirring at 80°C for three hours. The reaction liquor was cooled to room temperature, and saturated ammonium chloride aqueous solution was added, and the mixture was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution. After drying, the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 100/1) and the title compound was obtained as orange oily substance.

Step 2

Synthesis of 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H -benzimidazole

To chloroform 0.2 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde 22 mg, bis (2-methoxyethyl) amino sulphur trifluoride 0.036 ml was added, and the reaction liquor was heated with stirring at 80°C for eight hours. The solvent was eliminated by distillation under reduced pressure, then the residue was purified by preparative thin layer chromatography (Kieselgel TM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1), and the title compound was obtained as yellow solid.

Step 3

Production of 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole • monotrifluoroacetic acid salt

Trifluoroacetic acid 0.5 ml was added to 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole 12 mg, and the reaction liquor was stirred at room temperature for one hour. Trifluoroacetic acid was eliminated by distillation under reduced pressure, and thereafter the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as red oily substance.

1H-NMR(CD3OD) δ : 0.78-0.95 (4H, m), 1.91-2.15 (2H, m), 2.69 (3H, s), 5.38-5.43 (1H, m), 7.21-7.34 (4H, m), 7.52-7.63 (6H, m), 8.27-8.29 (1H, m).

ESI-MS (m/e): 449 (M+H).

Example 461

1-(2-(6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (3-chloro-4-methanesulphonyl) phenol, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.85-2.40 (4H, m), 2.90-3.27 (5H, m), 3.65-3.90 (2H, m), 5.15-5.43 (1H, m), 6.90-7.45 (5H, m), 7.84-8.15 (2H, m), 8.35-8.42 (1H, m), 8.60-8.68 (1H, m).

ESI-MS (m/e): 511 (M+H).

Example 462

2-(6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methanesulphonyl) phenoxy)-1H-benzimidazol-2-yl) (1,3) thiazolo (5,4-b) pyridine • monotrifluoroacetic acid salt

Using 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester obtained in Example 306 (Step 3) and (1,3) thiazolo (5,4-b) pyridine-2-carboxylic acid, the title compound was obtained as a yellow oily substance by the same process as in Example 306 (Step 4) and (Step 5), by a process based on these or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.60-2.40 (7H, m), 3.00-3.80 (5H, m), 5.00-5.60 (1H, m), 7.20-7.40 (2H, m), 7-25-7.80 (3H, m), 7.90-8,10 (2H, m), 8.40-8.80 (2H, m).

ESI-MS (m/e): 534 (M+H).

Example 463

5-(1-acetyl pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-(5-(trifluoromethyl)

pyridin-2-yl)-1H-benzimidazole

Using 5-(trifluoromethyl) pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 462, by a process based on this or a combination of these with a normal procedure.

1H-NMR(CDCl3) δ : 0.89 (1H, m), 1.22 (2H, m), 1.88-2.11 (3H, m), 2.27 (1H, m), 3.08 (3H, m), 3.63-3.76 (1H, m), 3.84 (1H, s), 5.38 (1H, dd, J = 25.8, 8.6 Hz), 7.11-7.20 (2H, m), 7.39 (1H, m), 7.54 (1H, m), 7.93 (2H, m), 8.11 (1H, m), 8.51 (1H, m), 8.93 (1H, m), 10.58-10.88 (1H, m).

ESI-MS (m/e): 545 (M+H).

Example 464

6-(1-acetyl pyrrolidin-2-yl)-2-(5-(difluoromethyl) pyridin-2-yl)-5-(4-methanesulphonyl) phenoxy)-1H-benzimidazole • monotrifluoroacetic acid salt

Using 5-(difluoromethyl) pyridine-2-carboxylic acid, the title compound was obtained as a yellow oily substance by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 0.92 (1H, m), 1.32 (2H, m), 1.89 (1H, m), 1.97-2.08 (2H, m), 2.13-2.14 (1H, m), 2.69 (3H, s), 3.16-3.17 (3H, s), 5.35 (1H, m), 7.30-7.32 (1H, m), 7.41-7.58 (1H, m), 7.60-7.62 (1H, m), 8.00-8.02 (3H, m), 8.04-8.22 (2H, m), 9.04 (1H, m).

ESI-MS (m/e): 527 (M+H).

Example 465

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl- 1H-benzimidazole • monotrifluoroacetic acid salt

To methanol 0.5 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol -5-yl) oxy) benzaldehyde 50 mg obtained in Example 460 (Step 1) was added hydroxylation boron sodium 7 mg under ice cooling, and the reaction liquor was stirred for one hour. Saturated ammonium chloride aqueous solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To dimethylformamide 1 ml solution of the obtained crude product, sodium hydride 10 mg and methyl iodide 0.030 ml were added successively and stirred at room temperature for 30 minutes. Saturated ammonium chloride aqueous solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Trifluoroacetic acid 0.5 ml was added to the obtained crude product, and the reaction liquor was

stirred at room temperature for two hours. Trifluoroacetic acid was eliminated by distillation under reduced pressure, and thereafter the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

1H-NMR(CD3OD) δ : 1.93 (1H, m), 2.07-2.11 (3H, m), 2.18 (2H, m), 2.45 (1H, m), 3.43 (3H, d, J = 3-1Hz), 3.75-3.95 (2H, m), 4.50 (d, 2H'J= 4-3 Hz), 5.49-5.56 (1H, m), 7.16 (3H, m), 7.44-7.49 (2H, m), 7.57 (1H, m), 7.70-7.73 (1H, m), 8.15 (1H, m), 8.27-8.30 (1H, m), 8.89 (1H, m).

ESI-MS (m/e): 443 (M+H).

Example 466

1-(4-(6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanol • monotrifluoroacetic acid salt

To tetrahydrofuran 1.3 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde 70 mg obtained in Example 460 (Step 1) was added methyllithium (1.0M diethyl ether solution) 0.4 ml at -78°C, and the reaction liquor was stirred at 78°C for 30 minutes. Saturated ammonium chloride solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Trifluoroacetic acid 0.5 ml was added to the obtained crude product and stirred at room temperature for 90 minutes, and thereafter, trifluoroacetic acid was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

1H-NMR(CD3OD) δ : 0.90-0.96 (1H, m), 1.31 (4H, m), 1.25-1.90 (3H, m), 2, 42 (1H, m), 2.68 (3H, s), 3.89-3.91 (1H, m), 5.50 (1H, m), 7.02-7.33 (4H, m), 7.42-7.52 (2H, m), 7.59-7.67 (1H, m), 8.10-8.14 (1H, m), 8.22-8.26 (1H, m), 8.80-8.87 (1H, m).

ESI-MS (m/e): 443 (M+H).

Example 467

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(3-methyl-[1,2,4]-oxadiazol-5-yl) phenoxy)-2-pyridin -2-yl-1H-benzimidazole

Using 5-(4-iodophenyl)-3-methyl-[1,2,4]-oxadiazole, the title compound was obtained as dark brown oily substance by the same process as in Example 122, a process based on this or a

combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.39-2.49 (10H, m), 3.42-3.88 (2H, m), 5.14-5.4 (1H, m), 6.70-8.69 (10H, m).

ESI-MS (m/e): 481 (M+H).

Example 468

(1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A

Step 1

Synthesis of 3-((t-butyl (dimethyl) silyl) oxy) dihydrofuran-2 (3H)-one

In 3-hydroxy dihydrofuran-2 (3H)-one 9.0 g dissolved in dimethylformamide 180 ml were added successively imidazole 9.0 g, t-butyldimethylsilyl chloride 15.9 g, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with ethyl acetate and was washed using water, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as colourless oily supplies.

Step 2

Synthesis of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-4-hydroxy butanoyl)-3-fluorophenyl) pyridine-2-carboxamide

In N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.1 g dissolved in tetrahydrofuran 100 ml, n-butyllithium (2.66M hexane solution) 3.1 ml was added dropwise at -78°C, and the reaction liquor was stirred at the same temperature for 15 minutes. 3-((t-butyl (dimethyl) silyl) oxy) dihydrofuran-2 (3H)-one 1.21 g was added to the reaction liquor, and the reaction liquor was stirred at the same temperature for one hour. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and it was warmed to room temperature, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1), and the title compound was obtained as a colourless oily substance.

Step 3

Synthesis of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-1,4-dihydroxy butyl)-3-fluorophenyl) pyridine-2-carboxamide

To methanol 20 ml solution of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-4-hydroxy butanoyl)-3-fluorophenyl) pyridine-2-carboxamide 860 mg was added sodium borohydride 114

mg under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1) and the title compound was obtained as a white solid.

Step 4

Synthesis of N-(4-(3-((t-butyl (dimethyl) silyl) oxy) pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide

Triethylamine 155 mg and methanesulfonyl chloride 130 mg were added under ice cooling successively to chloroform 8 ml solution of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-1,4-dihydroxybutyl)-3-fluorophenyl) pyridine-2-carboxamide 165 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 5 ml solution of the obtained residue was added sodium azide 25 mg, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and sodium borohydride 50 mg and copper sulfate • pentahydrate 5 mg were added successively to methanol 10 ml solution of the obtained residue, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, saturated aqueous sodium bicarbonate was added and was extracted with chloroform, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 50/1) and the title compound was obtained as a colourless oily substance.

Step 5

Synthesis of 1-acetyl-2-(2-fluoro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate

To methanol 1 ml solution of N-(4-(3-((t-butyl (dimethyl) silyl) oxy) pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide 59 mg was added 4 N hydrochloric acid-dioxane 2 ml, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and triethylamine 100 mg, acetic anhydride 90 mg, N,N-4-dimethylaminopyridine 5 mg were added successively to chloroform 5 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure and the obtained

residue was purified using silica gel chromatography (eluent: chloroform / methanol = 200/1), and obtained the title compound as a colourless oily substance.

Step 6

Synthesis of 1-acetyl-2-(2-fluoro-5-nitro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate diastereomer A and diastereomer B

Fuming nitric acid 1 ml was added to N-(4-(3-((t-butyl (dimethyl) silyl) oxy)-pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide 57 mg, and the reaction liquor was stirred at room temperature for 40 minutes. The reaction liquor was discharged into mixed solution of ice-saturated aqueous sodium bicarbonate and was extracted with chloroform, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel$^{TM}60F_{254}$, Art5744 (Merck Corporation), chloroform/methanol = 20/1), and respectively obtained diastereomer A and diastereomer B of the title compound as a yellow oily substance.

Step 7

Production of 1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin -2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A

Using 4-(methanesulphonyl) phenol and (1-acetyl-2-(2-fluoro-5-nitro -4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate diastereomer A, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.86-2.42 (8H, m), 3.04-3.10 (3H, m), 3.72-4.02 (2H, m), 5.06-5.38 (2H, m), 7.08-7.70 (5H, m), 7.83-7.97 (3H, m), 8.34-8.42 (1H, m), 8.61-8.68 (1H, m), 10.54-10.65 (1H, m).

ESI-MS (m/e): 535 (M+H).

Example 469

1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-ol diastereomer A

To methanol 2 ml solution of (1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A 14 mg obtained in Example 468 was added potassium carbonate 5 mg, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (Kieselgel$^{TM}60F_{254}$, Art5744 (Merck Corporation), chloroform/methanol = 15/1), and obtained the title compound as a white solid.

1H-NMR (CDCl3) δ : 1.82-2.47 (5H, m), 3.05&3.08 (3H, s), 3.70-3.97 (2H, m), 4.29-4.45 (1H, m), 5.00-5.32 (1H, m), 7.00-7.67 (5H, m), 7.81-7.96 (2H, m), 8.00-8.42 (1H, m), 8.60-8.69 (1H, m), 10.62-10.85 (1H, m).
ESI-MS (m/e): 493 (M+H).

Example 470

6-(1-acetyl-4,5-dihydro-1H-pyrrole-2-yl)-5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

To chloroform 1 ml solution of 1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-ol diastereomer A 2 mg obtained in Example 469 was added bis (2-methoxyethyl) amino sulphur trifluoride 2 mg, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Corporation), chloroform/methanol = 15/1), and obtained the title compound as a colourless oily substance.
1H-NMR (CDCl3) δ : 1.40-4.43 (10H, m), 7.03-7.80 (6H, m), 7.82-7.95 (3H, m), 8.32-8.46 (1H, m), 8.60-8.71 (1H, m), 10.38-10.60 (1H, m).
ESI-MS (m/e): 475 (M+H).

Example 471

1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer B

Using (1-acetyl-2-(2-fluoro-5-nitro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl) diastereomer B obtained in Example 468 (Step 6), the title compound was obtained by the same process as in Example 468 (Step 7), by a process based on this or a combination of these with a normal procedure.
1H-NMR (CDCl3) δ : 1.72-2.30 (8H, m), 3.02-3.08 (3H, m), 3.64-3.99 (2H, m), 5.26-5.47 (1H, m), 5.58-5.72 (1H, m), 7.09-7.73 (5H, m), 7.82-7.94 (3H, m), 8.33-8.43 (1H, m), 8.60-8.70 (1H, m), 10.47-10.68 (1H, m).
ESI-MS (m/e): 535 (M+H).

Example 472

1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-ol diastereomer B

Using (1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2 -yl-1H-benzimidazol -6-yl) pyrrolidin-3-yl acetate diastereomer B obtained in Example 471, the title compound was obtained by the same process as in Example 469, a process based on this or a combination of these with a normal procedure,.

1H-NMR (CDCl3) δ : 1.78-2.25 (5H, m), 3.03-3.10 (3H, m), 3.60-4.00 (2H, m), 4.50-4.68 (1H, m), 5.27-5.45 (1H, m), 7.03-7.73 (5H, m), 7.81-7.96 (3H, m), 8.32-8.45 (1H, m), 8.60-8.69 (1H, m), 10.51-10.82 (1H, m).
ESI-MS (m/e): 493 (M+H).

Example 473

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) piperidin-2-one

Using 1-(4-hydroxyphenyl) piperidin-2-one, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.
1H-NMR (CDCl3) δ : 1.74-2.62 (13H, m), 3.52-3.87 (4H, m), 5.18-5.36 (1H, m), 6.71-7.64 (7H, m), 7.76-7.90 (1H, m), 8.26-8.41 (1H, m), 8.56-8.68 (1H, m), 10.98-11.33 (1H, m).
ESI-MS (m/e): 496 (M+H).

Example 474

6-(1-acetyl pyrrolidin-2-yl)-5-((6-phenyl pyridin-3-yl) oxy)-2-pyridin -2-yl-1H-benzimidazole

Using 6-phenyl pyridin-3-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.
1H-NMR (CDCl3) δ : 1.40-2.50 (7H, m), 3.40-4.00 (2H, m), 5-20-5.60 (1H, m)-, 6.90-8.00 (11H, m), 8.20-8.45 (1H, m), 8.50-8.70 (2H, m), 10.60-10.90 (1H, m).
ESI-MS (m/e): 476 (M+H).

Example 475

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-fluorophenyl) pyridin-3-yl) oxy)-2-pyridin-2-yl -1H-benzimidazole

Using 6-(2-fluorophenyl) pyridin-3-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.
1H-NMR (CDCl3) δ : 1.60-2.50 (7H, m), 3.45-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.05 (10H, m), 8.30-8.45 (1H, m), 8.50-8.70 (2H, m), 10.80-11.20 (1H, m).
ESI-MS (m/e): 494 (M+H).

Example 476

1-(2-(6-(3-fluoro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (3-fluoro-4-methanesulphonyl) phenol, the title compound was obtained as yellow solid by

the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.87-2.38 (4H, m), 2.85-3.27 (5H, m), 3.60-3.95 (2H,,m), 5.20-5.41 (1H, m), 6.83-7.00 (1H, m), 7.28-7.40 (4H, m), 7.81-7.98 (2H, m), 8.35-8.42 (1H, m), 8.60-8.68 (1H, m).

ESI-MS (m/e): 495 (M+H).

Example 477

1-(4-{(6-(1-acetyl pyrrolidin-2-yl)-2-pyridine-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy} phenyl) pyrrolidin-2-one

Using 1-(4-hydroxyphenyl) pyrrolidin-2-one, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.80-2.40 (6H, m), 2.62 (2H, m), 3.55-3.95 (4H+1/2H, m), 5.28 (1/2H, $ m), 6.90-7.10 (3H, m), 7.35 (1H+1/2H, m), 7.45-7.65 (2H+1/2H, m), 7.85 (1H, m), 8.34 (1H, m), 8.61 (1H, m), 10.4-10.8 (1H, br).

ESI-MS (m/e): 482 (M+H).

Example 478

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyridine-2 (1H)-one

Using 1-(4-hydroxyphenyl) pyridine-2 (1H)-one, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

1H-NMR (CDCl3) δ : 1.72-2.42 (7H, m), 3.48-3.86 (2H, m), 5.15-5.52 (1H, m), 6.19-6.32 (1H, m), 6.61-6.73 (1H, m), 6.80-7.66 (9H, m), 7.77-7.89 (1H, m), 8.32-8.41 (1H, m), 8.52-8.65 (1H, m), 11.07-11.48 (1H, m).

ESI-MS (m/e): 492 (M+H).

Example 479

5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2,2'-bipyridine • monotrifluoroacetic acid salt

Using 2,2'-bipyridine-5-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.80-2.80 (7H, m), 3.160-4.05 (2H, m), 5.20-5.60 (1H, m), 7.50-7.90 (4H, m), 8.00-8.15 (1H, m), 8.15-8.25 (1H, m), 8.30-8.40 (1H, m), 8.45-8.60 (1H, m), 8-60-9.00 (5H, m).

ESI-MS (m/e): 477 (M+H).

Example 480

N-(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-methane sulfonamide

Using 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole obtained in Example 162 (Step 7) and N-t-butoxycarbonyl-glycine, the title compound was obtained by the same procedures as in Example 171 and Example 178, a process based on these or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.93-2.14 (3H, m), 2.06-2.27 (1H, m), 2.86 and 2.95 (total 3H, each s), 3.13 (3H, s), 3.43-4.08 (4H, m), 5.20-5.38 (1H, m), 7.20-7.60 (5H, m), 7.93-8.02 (3H, m), 8.23-8.30 (1H, m), 8.74 (1H, brs).

ESI-MS (m/e): 570 (M+H).

Example 481

(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-ethyl carbamate ester

Using 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole obtained in Example 162 (Step 7) and N-t-butoxycarbonyl-glycine, the title compound was obtained by the same procedures as in Example 171 and Example 181, a process based on these or a combination of these with a normal procedure.

1H-NMR(CD3OD) δ : 1.18 and 1.23 (total 3H, each t, J = each 7.1 Hz), 1.93-2.14 (3H, m), 2.22-2.44 (1H, m), 3.12 and 3.13 (total 3H, each s), 3.30-4.13 (6H, m), 5.24-5.33 (1H, m), 7.20-7.60 (5H, m), 7.93-8.01 (3H, m), 8.28 (1H, t, J = 8.2 Hz), 8.73 (1H, brs).

ESI-MS (m/e): 564 (M+H).

Example 482

6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

Step 1

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2- carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide 100 mg obtained by Example 338 (Step 4) was optically-resolved by a column for optical resolution (CHIRALPAK OD 2 cmϕ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 60/40/0.1, flow rate: 10 ml/min), and enantiomer A (retention time: 17.8 min), enantiomer B (retention time: 21.0 min) were respectively obtained as pale yellow solid.

Step 2

Production of 6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin -2-yl-1H-benzimidazole enantiomer A

Using N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer A obtained in Example 482 (Step 1) and 4-brumo(sic)phenol, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

1H-NMR, (CDCl3) δ : 1.56-2.41 (7H, m), 3.42-3.90 (2H, m), 5.16-5.51 (1H, m), 6.78-7.66 (7H, m), 7.80-7.93 (1H, m), 8.32-8.44 (1H, m), 8.54-8.67 (1H, m), 11.14-11.65 (1H, m).

ESI-MS (m/e): 479 (M+H).

Example 483

6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

Using N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 482 (Step 1) and 4-brumo(sic)phenol, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

ESI-MS (m/e): 479 (M+H).

Examples 484

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4],-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.51-2.43 (7H, m), 2.59-2.74 (3H, m), 3.50-3.93 (2H, m), 5.17-5.46 (1H, m), 7.00-7.72 (4H, m), 7.82-8.13 (2H, m), 8.34-8.44 (1H, m), 8.57-8.69 (2H, m), 10.75-11.14 (1H, m).

ESI-MS (m/e): 482 (M+H).

Example 485

5-(1-acetyl-3-methylpyrrolidin-2-yl)-6-(4-(methylsulphonyl) phenoxy)-2-pyridin-2-yl-1H -benzimidazole

Step 1

Synthesis of N-(3-fluoro-4-[2-(2-hydroxyethyl) acryloyl) phenyl) pyridine-2-carboxamide

To N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.0 g dissolved in tetrahydrofuran 20 ml solution, 60 % sodium hydride 136 mg was added under ice cooling, and the reaction liquor was

stirred at the same temperature for 15 minutes. The reaction liquor was cooled to -78°C, and thereafter, n-butyllithium (2.66M hexane solution) 1.53 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 30 minutes. 3-methylene dihydro-furan-2(3H)-one 0.36 ml was added to the reaction liquor at the same temperature, and the reaction liquor was stirred at the same temperature for two hours, and thereafter, it was warmed to 0°C, and it was stirred for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and the mixture was extracted with ethyl acetate, and the organic layer was washed using saturated aqueous sodium chloride solution, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 3/1) and the title compound was obtained as a colourless oily substance.

Step 2

Synthesis of N-(4-[1,4-dihydroxy-2-methyl butyl)-3-fluorophenyl) pyridine-2-carboxamide

To methanol 8 ml solution of N-(3-fluoro-4-(2-[2-hydroxyethyl) acryloyl) phenyl) pyridine-2-carboxamide 320 mg, sodium borohydride 150 mg was added, and the reaction liquor was stirred at room temperature for one hour. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform / methanol =100/1) and the title compound was obtained as a colourless oily substance.

Step 3

Synthesis of N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide

To chloroform 5 ml solution of N-(4-(1,4-dihydroxy-2-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide 100 mg were added successively triethylamine 0.18 ml, methanesulfonyl chloride 0.07 ml, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 4 ml solution of the obtained residue was added sodium azide 23 mg, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled to room temperature, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and, to methanol 5 ml solution of the obtained residue were added successively sodium borohydride 50 mg, copper sulfate • pentahydrate 5 mg, and the reaction liquor was stirred at 40°C for 15 minutes. The reaction liquor was cooled to room temperature, and thereafter, saturated aqueous sodium bicarbonate was added, extraction was carried out with chloroform and dried with anhydrous

sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 4 ml solution of the obtained residue were added successively triethylamine 0.08 ml, acetic anhydride 0.07 ml, N,N-4-dimethylaminopyridine 5 mg, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform / methanol = 100/1) and the title compound was obtained as a colourless oily substance.

Step 4

Synthesis of N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide

Fuming nitric acid 1 ml was added to N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-3- fluorophenyl) pyridine-2-carboxamide 70 mg, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was discharged into ice-saturated aqueous sodium bicarbonate mixed solution, extracted with chloroform, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and thereby obtained the title compound as yellow solid.

Step 5

Production of 5-(1-acetyl-3-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide and 4-(methanesulphonyl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 0.81-2.73 (9H, m), 3.03-3.11 (3H, m), 3.36-3.99 (2H, m), 4.65-5.43 (1H, m), 7.00-7.75 (5H,), 7.81-7.79 (3H, m), 8.32-8.45 (1H, m), 8.60-8.68 (1H, m), 10.51-10.82 (1H, br).

ESI-MS (m/e): 491 (M+H).

Example 486

6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-3,4-dihydro-naphthalene-1(2H)-one

Using 6-hydroxy-3,4-dihydro-naphthalene-1 (2H)-one, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.00-3.00 (13H, m), 3.40-3.95 (2H, m), 5.00-5.50 (1H, m), 6.60-7.80 (5H, m), 7.80-8.20 (2H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m), 10.80-11.20 (1H, m).
ESI-MS (m/e): 467 (M+H).

Example 487

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1H-imidazol-1-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole
Using 4-(1H-imidazol-1-yl) phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.00-2.50 (7H, m), 3.50-4.50 (2H, m), 5.20-6.00 (1H, m), 6.80-8.80 (13H, 13).
ESI-MS (m/e): 465 (M+H).

Example 488

6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-1-methyl-[1,2,3,4)-tetrahydronaphthalene-1-ol
To tetrahydrofuran 0.5 ml solution of 6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-3,4-dihydro-naphthalene-1 (2H)-one 7 mg obtained in Example 486 was added methylmagnesium bromide (5.0M tetrahydrofuran solution) 0.050 ml under ice cooling, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with chloroform, washed with saturated ammonium chloride aqueous solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound was obtained as a colourless oily substance.
^{1}H-NMR ($CDCl_3$) δ : 1.10-2.80 (16H, m), 3.50-4.00 (2H, m), 5.10-5.50 (1H, m), 6.60-7.90 (7H, m), 8.30-8.50 (1H, m), 8.50-70 (1H, m).
ESI-MS (m/e): 465 (M+H).

Example 489

6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-[1,2,3,4]-tetrahydronaphthalene-1-ol
To tetrahydrofuran 0.5 ml solution of 6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-3,4-dihydro-naphthalene-1 (2H)-one 7 mg obtained in Example 486 was added sodium borohydride 5 mg under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with chloroform, washed with saturated ammonium chloride aqueous solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced

pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a colourless oily substance.
^{1}H-NMR ($CDCl_3$) δ : 1.00-2.50 (14H, m), 4.00-6.00 (3H, m), 6.80-8.50 (9H, m).
ESI-MS (m/e): 469 (M+H).

Example 490

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer A

Step 1

Synthesis of ethyl (2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoate

Tetrahydrofuran 40 ml solution of (diethoxy phosphoryl) (fluoro) ethyl acetate 2.0 g was cooled to -78°C, and thereafter, n-butyllithium (2.66M hexane solution) 3.4 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 15 minutes. To the reaction liquor was added ((t-butyl (dimethyl) silyl) oxy) acetaldehyde 2.1 ml, and the reaction liquor was stirred at the same temperature for two hours. Saturated aqueous sodium bicarbonate was added to the reaction solution at the same temperature, and it was warmed to room temperature, and thereafter, extraction was carried out with ethyl acetate. It was dried using anhydrous sodium sulfate, and next the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 50/1) and the title compound was obtained as a colourless oily substance.

Step 2

Synthesis of N-(4-((2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoyl)-3-fluorophenyl) pyridine-2-carboxamide

To N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.0 g dissolved in tetrahydrofuran 40 ml solution, 60 % sodium hydride 136 mg was added under ice cooling, and the reaction liquor was stirred at the same temperature for 20 minutes. The reaction liquor was cooled to -78°C, and thereafter, n-butyllithium (2.66M hexane solution) 1.53 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 20 minutes. Ethyl (2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoate 1.07 g was added to the reaction liquor at the same temperature, and the reaction liquor was stirred at the same temperature for four hours. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and it was warmed to room temperature, and thereafter, it was extracted with ethyl acetate, and the organic layer was washed using saturated aqueous sodium chloride solution, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 3/1) and the title

compound was obtained as a colourless oily substance.

Step 3

N-(4-(4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro-1-hydroxy butyl)-3-fluorophenyl) pyridine-2-carboxamide

To methanol 20 ml solution of N-(4-((2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro but-2-enoyl)-3-fluorophenyl) pyridine-2-carboxamide 300 mg was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for four hours. The catalyst was filtered, and the solvent was eliminated by distillation under reduced pressure, and, to methanol 4 ml solution of the obtained residue was added sodium borohydride 50 mg, and the reaction liquor was stirred at room temperature for one hour.

Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1) and the title compound was obtained as a colourless oily substance.

Step 4

Synthesis of N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereoisomer A and diastereomer B

To chloroform 5 ml solution of N-(4-(4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro-1-hydroxybutyl)-3-fluorophenyl) pyridine-2-carboxamide 100 mg were added successively triethylamine 46 mg, methanesulfonyl chloride 39 mg, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 4 ml solution of the obtained residue was added sodium azide 22 mg, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and tetrabutyl ammonium fluoride (1.0M tetrahydrofuran solution) 0.3 ml was added to tetrahydrofuran 4 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for one hour. To the reaction liquor, water was added and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 5 ml solution of the obtained residue were added successively triethylamine 46 mg, methanesulfonyl chloride 39 mg,

and the reaction liquor was stirred at room temperature for 30 minutes. To the reaction liquor, saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and copper sulfate • pentahydrate 10 mg, sodium borohydride 50 mg were added successively to methanol 4 ml solution of the obtained residue, and the reaction liquor was stirred at 40°C for one hour. The reaction liquor was cooled, and thereafter, saturated aqueous sodium bicarbonate was added, and extraction was carried out with chloroform and the chloroform layer was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 4 ml solution of the obtained residue were added successively triethylamine 46 mg, acetic anhydride 35 mg, N,N-4-dimethylaminopyridine 5 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using preparative thin layer chromatography (chloroform/methanol = 30/1) and the title compounds diastereomer A and diastereomer B were respectively obtained as a colourless oily substance.

Step 5

Production of 5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer A

Fuming nitric acid 0.5 ml was added to N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereomer A 18 mg, and the reaction liquor was stirred at room temperature for ten minutes. The reaction liquor was discharged into ice-saturated aqueous sodium bicarbonate mixed solution, extracted with chloroform, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Using the obtained composition(sic) product and 4-(methanesulphonyl) phenol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.85-2.40 (5H, m), 3.06 and 3.09 (3H, s), 3.79-4.08 (2H, m), 4.96-5.62 (2H, m), 7.05-7.70 (5H, m), 7.83-7.99 (3H, m), 8.34-8.43 (1H, m), 8.61-8.69 (1H, m), 10.58-10.84 (1H, m).

ESI-MS (m/e): 495 (M+H).

Example 491

6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-(4-(2-thienyl) phenoxy)-1H-benzimidazole

Using 4-(2-thienyl) phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.05-2.45 (7H, m), 3.40-4.00 (2H, m), 5.10-5.60 (1H, m), 6.80-8.00 (11H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m).
ESI-MS (m/e): 481 (M+H).

Example 492-
2-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1H-iso indole-1,3 (2H)-dione
Using 2-(4-hydroxyphenyl)-1H-iso indole-1,3 (2H) dion, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.05-2,40 (7H, m), 3.40-4.05 (2H, m), 5.05-5.60 (1H, m), 6.80-8.20 (12H, m), 8.30-8.70 (2H, m).
ESI-MS (m/e): 544 (M+H).

Example 493
5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer B
Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereomer B obtained by Example 490 (Step 4), the title compound was obtained as pale yellow solid in accordance with Example 490 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.80-2.45 (5H, m), 3.05 and 3.08 (3H, s), 3.61-4.31 (2H, m), 5.08-5.54 (2H, m), 7.03-7.80 (5H, m), 7.81-7.97 (3H, m), 8.33-8.43 (1H, m), 8.60-8.68 (1H, m), 10.52-10.75 (1H, 1).
ESI-MS (m/e): 495 (M+H).

Example 494
6-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-1H-tetrazol-1-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole
Using 4-(5-methyl-1H-tetrazol-1-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR(CD_3OD) δ: 1.91 and 2.15 (total 3H, each s), 1.97-2.20 (3H, m), 2.22-2.58 (1H, m), 2.63 and 2.64 (total 3H, each s), 3.62-4.00 (2H, m), 5.34-5.42 (1H, m), 7.22-7.68 (7H, m), 7.94-8.05 (1H, m), 8.30 (1H, t, J = 7.8 Hz), 8.76 (1H, brs).
ESI-MS (m/e): 481 (M+H).

Example 495

Ethyl 5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridine-2-carboxylate

Using ethyl 5-hydroxypyridine-2-carboxylate, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.30-1.50 (3H, m), 1.50-2.50 (7H, m), 3.50-3.90 (2H, m), 4.35-4.60 (2H, m), 5.10-5.45 (1H, m), .6.90-7.70 (4H, m), 7.80-7.95 (1H, m), 8.00-8.20 (1H, m), 8.30-8.80 (3H, m), 10.60-11.20 (1H, m).

ESI-MS (m/e): 472 (M+H).

Example 496

6-(1-acetyl pyrrolidin-2-yl)-5-(4-pyrazin-2-yl phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-pyrazin-2-yl phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 0.80-2.40 (7H, m), 3.60-3.90 (2H, m), 5.20-5.60 (1H, m), 6.80-8.05 (8H, m), 8.30-8.80 (4H, m), 8.90-9.10 (1H, m), 10.40-10.80 (1H, m).

ESI-MS (m/e): 477 (M+H).

Example 497

6-(1-acetyl pyrrolidin-2-yl)-5-(1H-indol-5-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 1H-indole-5-ol, title-compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.20-2.40 (7H, m), 3.60-4.00 (2H, m), 5.20-5.60 (1H, m), 6.40-6.60 (1H, m), 6.80-8.00 (7H, m), 8.20-8.50 (2H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 438 (M+H).

Example 498

(2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine

Step 1

Synthesis of (3-fluoro-4-pyrrolidin-2-yl phenyl) amine dihydrochloride

To mixed solution of methanol 50 ml and ethyl acetate 50 ml of 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 19 g obtained in Example 338 (Step 2) was added 4 N hydrochloric acid-dioxane solution 100 ml under ice cooling, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid.

Step 2

Synthesis of 2,2,2-trifluoro-N-(3-fluoro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide

To (3-fluoro-4-pyrrolidin-2-yl phenyl) amine dihydrochloride 20 g suspended in chloroform 200 ml were added successively pyridine 39 ml and trifluoroacetic anhydride 24 ml under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as brown oily substance.

Step 3

Synthesis of 2,2,2-trifluoro-N-(5-fluoro-2-nitro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide

Fuming nitric acid 100 ml was added under ice cooling to 2,2,2-trifluoro-N-(3-fluoro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide 28 g, and the reaction liquor was stirred at room temperature for one hour. Iced water was added to the reaction liquor and, after dilution, it was extracted with ethyl acetate and washed using saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 10/1) and the title compound was obtained as a yellow oily substance.

Step 4

Synthesis of t-butyl 2-(4-amino-2-fluoro-5-nitrophenyl) pyrrolidine-1-carboxylate

To 2,2,2-trifluoro-N-(5-fluoro-2-nitro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide 29 g dissolved in tetrahydrofuran 150 ml, were added 1N sodium hydroxide aqueous solution 150 ml under ice cooling, and the reaction liquor was stirred at room temperature for five hours. Furthermore, di t-butyl dicarbonate 23 ml was added to the reaction liquor and the reaction liquor was stirred for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as a yellow solid

Step 5

Synthesis of t-butyl 2-(4-amino-2-((2'-fluorobiphenyl-4-yl) oxy)-5-nitrophenyl) pyrrolidine-1-carboxylate

To N,N-dimethylformamide 3 ml solution of t-butyl 2-(4-amino-2-fluoro-5-nitrophenyl) pyrrolidine-1-carboxylate 288 mg were added 2'-fluorobiphenyl-4-ol 200 mg and potassium carbonate 184 mg, and the reaction liquor was stirred overnight at 80°C. The reaction liquor was diluted with ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as a yellow solid

Step 6

Synthesis of t-butyl 2-(4,5-diamino-2-((2'-fluorobiphenyl-4-yl) oxy) phenyl) pyrrolidine-1-carboxylate

To methanol 5 ml solution of t-butyl 2-(4-amino-2-((2'-fluorobiphenyl-4-yl) oxy)-5-nitrophenyl) pyrrolidine-1-carboxylate 410 mg was added development Raney nickel catalyst 1 ml, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for a whole day. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained as brown oily substance.

Step 7

Synthesis of 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole

To methanol 5 ml solution of t-butyl 2-(4,5-diamino-2-((2'-fluorobiphenyl-4-yl) oxy) phenyl) pyrrolidine-1-carboxylate 255 mg were added N-((IE)-pyridin-2-ylmethylene) aniline (1M methanol solution) 1.6 ml, and the reaction liquor was stirred at 90°C for a whole day. The reaction liquor was diluted with ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and 4 N hydrochloric acid-dioxane solution 5 ml was added to the obtained residue 332 mg, and the reaction liquor was stirred at room temperature for three hours. The solvent was eliminated by distillation under reduced pressure, and extraction was carried out with chloroform after dilution with saturated aqueous sodium bicarbonate. The organic layer was washed using saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was refined by silica gel column chromatography (eluent: chloroform-methanol / ammonia water solution = 20/1/0.1) and the title compound was obtained as a yellow oily substance.

Step 8

Production of (2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine

To pyridine 1 ml solution of 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2 -yl-1H-benzimidazole 37 mg were added successively N-(t-butoxy carbonyl)-N-methylglycine 19 mg, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 24 mg, and the reaction liquor was stirred at room temperature for three hours. 4 N hydrochloric acid-dioxane solution 2 ml was added to the reaction liquor, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with chloroform, and it was made basic with saturated aqueous sodium bicarbonate. Thereafter, the organic layer was washed using saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 10/1) and the title compound was obtained as a straw-coloured solid.

^{1}H-NMR($CDCl_3$) δ : 1.60-2.60 (6H, m), 2.80-3.05 (1H, m), 3.10-4.00 (4H, m), 5.20-5.60 (1H, m), 6.95-7.70 (11H, m), 7-75-7.95 (1H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 522 (M+H).

Example 499

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,3,4]-oxadiazol-2-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,3,4]-oxadiazol-2-yl) pyridin-3-ol, the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.40-2.40 (7H, m), 2.50-2.80 (3H, m), 3.50-3.95 (2H, m), 5.05-5.50 (1H, m), 6.80-7.80 (4H, m), 7.80-8.00 (1H, m), 8.05-8.30 (1H, m), 8.30-8.50 (1H, m), 8.50-8.80 (2H, m), 10.50-11,00(1H, m).

ESI-MS (m/e): 482 (M+H).

Example 500

6-(1-acetyl pyrrolidin-2-yl)-5-((6-([1,3,4]-oxadiazol-2-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-([1,3,4]-oxadiazol-2-yl) pyridin-3-ol, the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.40-2.40 (7H, m), 3.50-3.95 (2H, m), 5.05-5.50 (1H, m), 6.80-7.80 (4H, m), 7.80-8.00 (1H, m), 8.05-8.80 (5H, m), 10.50-11.00 (1H, m).

ESI-MS (m/e): 468 (M+H).

Example 501

6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-(4-pyrimidin-2-yl phenoxy)-1H-benzimidazole

Using 4-pyrimidin-2-yl phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.90 and 2.13 (total 3H, each s), 1.94-2.53 (4H, m), 3.62-3.80 (1H, m), 3.80-4.00 (1H, m), 5.38-5.46 (1H, m), 7.16-7.56 (6H, m), 7.95-8.04 (1H, m), 8.24-8.33 (1H, m), 8.46 (2H, d, J = 9.0 Hz), 8.70-8.79 (1H, m), 8.83-8.85 (2H, m).

ESI-MS (m/e): 477 (M+H).

Example 502

1-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methyl) pyrrolidine-2,5-dione

Using 1-((5-hydroxypyridin-2-yl) methyl) pyrrolidine-2,5-dione, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.80-2.46 (7H, m), 2.74-2.86 (4H, m), 3.53-3.90 (2H, m), 4.76-4.87 (2H, m), 5.18-5.48 (1H, m), 6.76-7.67 (5H, m), 7.80-7.91 (1H, m), 8.28-8.44 (2H, m), 8.57-8.67 (1H, m), 11.07-11.41 (1H, m).

ESI-MS (m/e): 511 (M+H).

Example 503

6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-((6-(5-(trifluoromethyl) -[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-1H-benzimidazole

Using 6-(5-(trifluoromethyl)-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.89-2.54 (7H, m), 3.84-4.01 (2H, m), 5.32-5.42 (1H, m), 7.20-7.80 (4H, m), 7.98-8.03 (1H, m), 8.24-8.37 (2H, m), 8.60-8.65 (1H, m), 8.73-8.80 (1H, m).

ESI-MS (m/e): 536 (M+H).

Example 504

6-(1-acetyl pyrrolidin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H,

m), 7.80-8.50 (3H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).
ESI-MS (m/e): 434 (M+H).

Example 505

6-(1-acetyl pyrrolidin-2-yl)-5-((6-bromopyridin-3-yl) oxy)-2-pyridin-2-yl- 1H-benzimidazole

Using 6-bromopyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H, m), 7.70-8.00 (1H, m), 8.05-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).
ESI-MS (m/e): 478, 480 (M+H).

Example 506

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methoxypyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methoxypyridin-3-ol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.60 (7H, m), 3.50-4.10 (5H, m), 5.10-5.70 (1H, m), 6.60-7.70 (5H, m), 7.70-7.95 (1H, m), 7.95-8.10 (1H, m), 8.25-8.45 (1H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).
ESI-MS (m/e): 430 (M+H).

Example 507

5-((2'-fluorobiphenyl-4-yl) oxy)-6-(1-(methanesulphonyl) pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazole

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 498 (Step 7), the title compound was obtained as colourless oil substance by the same process as in Example 178, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 2.70-3.00 (3H, m), 3.40-3.80 (2H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).
ESI-MS (m/e): 529 (M+H).

Example 508

Methyl 2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxylate

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole

obtained in Example 498 (Step 7), the title compound was obtained as a colourless oily substance by the same process as in Example 181, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 3.40-3.80 (5H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.8 (1H, m).

ESI-MS (m/e): 509 (M+H).

Example 509

2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)-N,N-dimethylpyrrolidine-1-carboxamide

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 498 (Step 7), the title compound was obtained as a white solid in accordance with Example 336 (Step 1) (Step 2), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR($CDCl_3$) δ : 1.60-2.20 (3H, m), 2.20-2.50 (1H, m), 2.72 (3H, s), 2.84 (3H, s), 3.40-3.80 (2H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 522 (M+H).

Example 510

1-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methyl) pyrrolidin-2-one

Using 1-((5-hydroxypyridin-2-yl) methyl) pyrrolidin-2-one, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1-80-2.57 (11H, m), 3.33-3.89 (4H, m), 4.48-4.64 (2H, m), 5.20-5.51 (1H, m), 6.77-7.67 (5H, m), 7.77-7.90 (1H, m), 8.27-8.42 (2H, m), 8.56-8.66 (1H, m), 11.16-11.53 (1H, m).

ESI-MS (m/e): 497 (M+H).

Example 511

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(3-methyl-1H-[1,2,4]-triazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(3-methyl-1H-[1,2,4]-triazol-5-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.76-2.82 (10H, m), 3.50-3.90 (2H, m), 5.13-5.59 (1H, m), 6.64-8.04 (8H, m), 8.23-8.64 (2H, m).

ESI-MS (m/e): 480 (M+H).

Example 512

6-(1-(difluoro acetyl) pyrrolidin -2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using difluoro acetic acid, the title compound was obtained as a white solid in accordance with Example 498 (Step 8), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.80-2.50 (4H, m), 3.60-4.20 (2H, m), 5.20-6.20 (2H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 529 (M+H).

Example 513

2-2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl acetate

Using acetoxy acetic acid, the title compound was obtained as a yellow oily substance in accordance with Example 498 (Step 8), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.40 (7H, m), 3.40-4.00 (2H, m), 4.05-4.80 (2H, m), 5.10-5.60 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 551 (M+H).

Example 514

(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methanol

To tetrahydrofuran 2 ml solution of ethyl 5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridine-2-carboxylate 90 mg obtained in Example 495 was added lithium aluminium hydride 20 mg under ice cooling, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with chloroform, washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

^{1}H-NMR($CDCl_3$) δ : 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 4.70-4.85 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H, m), 7.70-7.95 (1H, m), 8.30-8.50 (2H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 430 (M+H).

Example 515

2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol

To methanol solution 0.5 ml of 2-(2-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl acetate 11 mg obtained in Example 513 was added potassium carbonate 10 mg, and the reaction liquor was stirred at room temperature for one day. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel$^{TM}60F_{254}$, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 1.40-2.50 (4H, m), 3.40-4.20 (4H, m), 5.05-5.70 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 509 (M+H).

Example 516

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(fluoromethyl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

To chloroform 1 ml solution of (5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methanol 17 mg obtained in Example 514, bis (2-methoxyethyl) amino suphur tri fluroride 0.050 ml was added under ice cooling, and the reaction liquor was stirred at 0°C for two hours. The reaction liquor was diluted with chloroform, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solventwas eliminated by distillation under the reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel$^{TM}60F_{254}$, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as slight yellow solid.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 5.05-5.60 (3H, m), 6.80-7.70 (5H, m), 7.70-7.95 (1H, m), 8.30-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 432 (M+H).

Example 517

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(3-methyl-[1,2,4]-oxadiazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(3-methyl [1,2,4]-oxadiazol-5-yl) pyridin-3-ol, the title compound was obtained as an

oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.65-2.57 (10H, m), 3.48-3.93 (5H, m), 5.17-5.52 (1H, m), 6.82-7.67 (7H, m), 7.80-7.91 (1H, m), 8.34-8.44 (1H, m), 8.57-8.67 (1H, m), 11.32-11.68 (1H, m).
ESI-MS (m/e): 482 (M+H).

Example 518

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1-methyl-1H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1-methyl-1H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same method as in Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.83-2.40 (7H, m), 3.58-3.90 (2H, m), 4.15 and 4.19 (total 3H, each s), 5.16-5.48 (1H, m), 6.93-7.78 (7H, m), 7.80-7.91 (1H, m), 8.34-8.42 (1H, m), 8.56-8.65 (1H, m).
ESI-MS (m/e): 481 (M+H).

Example 519

5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-N-methylpyridine-2-carboxamide

Using 5-hydroxy-N-methylpyridine-2-carboxamide, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.60-2.50 (7H, m), 2.90-3.10 (3H, m), 3.50-4.00 (2H, m), 5.05-5.50 (1H, m), 6.80-7.70 (3H, m), 7.70-8.00 (2H, .m), 8.10-8.50 (3H, m), 8.50-8.70 (1H, m).
ESI-MS (m/e): 457 (M+H).

Example 520

3-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl)-1,3-oxazolidin-2-one

Using 3-(5-hydroxypyridin-2-yl)-1,3-oxazolidin-2-one, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.60-2.50 (7H, m), 3.50-4.00 (2H, m), 4.10-4.35 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (4H, m), 7.70-8.00 (1H, m), 8.10-8.50 (3H, m), 8.50-8.70 (1H, m), 10.70-11.10 (1H, m).
ESI-MS (m/e): 485 (M+H).

Example 521

6-(1-acetyl pyrrolidin-2-yl)-5-(6-methylpyridin-3-yl sulphanyl)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridine-3-thiol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.20-2.50 (10H, m), 3.50-4.00 (2H, m), 5.20-5,60(1H, m), 6.80-8.00 (6H, m), 8.20-8.70 (3H, m).

ESI-MS (m/e): 430 (M+H).

Example 522

5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) nicotinic acid methyl ester

Using 5-hydroxy nicotinic acid methyl ester, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.89 and 2.14 (total 3H, each s), 1.96-2.20 (3H, m), 2.32-2.54 (11H, m), 3.63-3.90 (2H, m), 3.93 (3H, s), 5.37-5.41 (1H, m), 7.20-7.57 (3H, m), 7.92-8.03 (2H, m), 8.30 (1H, t, J = 8.4 Hz), 8,65-8.67 (1H, m), 8.74-8.78 (1H, m), 8.89-8.92 (1H, m).

ESI-MS (m/e): 458 (M+H).

Example 523

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(methylthio) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylthio pyridin-3-ol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.70 (10H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.10 (6H, m), 8.20-8.50 (2H, m), 8.50-8.70 (1H, m), 10.70-11.10 (1H, m).

ESI-MS (m/e): 446 (M+H).

Example 524

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,3-dimethyl-1H-[1,2,4]-triazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1,3-dimethyl-1H-[1,2,4]-triazol-5-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.79-2.2.53 (10H, m), 3.50-3.90 (5H, m), 5.19-5.30 (1H, m), 6.87-7.66 (5H, m), 7.77-7.91 (1H, m), 7.96-8.10 (2H, m), 8.33-8.43 (1H, m), 8.56-8.67 (1H, m), 10.82-11.08 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 525

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,5-dimethyl-1H-[1,2,4]-triazol-3-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1,5-dimethyl-1H-[1,2,4]-triazol-3-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.79-2.53 (10H, m), 3.50-3.90 (5H, in), 5.19-5.30 (1H, m), 6.87-7.66 (5H, m), 7.77-7.91 (1H, m), 7.96-8.10 (2H, m), 8.33-8.43 (1H, m), 8.56-8.67 (1H, m), 10.82-11.08 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 526

6-(1-acetyl pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester obtained in Example 338 (Step 2), pyrazine-2-carboxylic acid and 2'-fluorobiphenyl-4-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 3), (Step 5), a process based on these or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.20-2.50 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.80 (10H, m), 8.50-8.90 (2H, m), 9.40-10.00 (1H, m), 10.50-11.20 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 527

6-(1-acetyl pyrrolidin-2-yl)-5-((5-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 5-chloro-3-pyridinol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.89 and 2.15 (total 3H, each s), 1.94-2.20 (3H, m), 2.29-2.49 (1H, m), 3.62-3.97 (2H, m), 5.32-5.40 (1H, m), 7.17-7.63 (4H, m), 7.94-8.04 (1H, m), 8.26-8.41 (3H, m), 8.73-8.79 (1H, m).

ESI-MS (m/e): 434 (M+H).

Example 528

1-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) pyrrolidin-2-one

Using 1-(5-hydroxypyridin-2-yl) pyrrolidin-2-one, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of

these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.79-2.43 (9H, m), 2.58-2 71(2H, m), 3.53-3.89 (2H, m), 3.98-4.17 (2H, m), 5.21-5.57 (1H, m), 6.77-7.57 (4H, m), 7.74-8.66 (5H, m).
ESI-MS (m/e): 483 (M+H).

Example 529

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole
Using 6-methylpyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.60-2.60 (10H, m), 3.50-3.95 (2H, m), 5.20-5.60 (1H, m), 6.65-7.80 (4H, m), 8.20-8.40 (1H, m), 8.50-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.40 (1H, m).
ESI-MS (m/e): 415 (M+H).

Example 530

6-(1-acetyl pyrrolidin-2-yl)-5-((6-[[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole
Using 6-([1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.80-2.43 (7H, m), 3.57-3.92 (2H, m), 5.19-5.46 (1H, m), 6.98-8.43 (7H, m), 8.55-8.87 (3H, m), 10.53-10.74 (1H, m).
ESI-MS (m/e): 468 (M+H).

Example 531

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,3-oxazol-4-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole
Using 4-(1,3-oxazol-4-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR(CD_3OD) δ : 1.89-2.20 (6H, m), 2.28-2.50 (1H, m), 3.62-4.00 (2H, m), 5.39-5.50 (1H, m), 7.12-7.53 (5H, m), 7.80-7.89 (2H, m), 7.93-8.04 (1H, m), 8.24-8.33 (3H, m), 8.70-8.79 (1H, m).
ESI-MS (m/e): 466 (M+H).

Example 532

6-(1-acetyl pyrrolidin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole
Using 6-chloropyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 526, a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.20-5.60 (1H, m), 6.65-8.30 (5H, m), 8.40-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.60 (1H, m).
ESI-MS (m/e): 435 (M+H).

Example 533

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR(CD_3OD) δ : 1.90-2.19 (6H, m), 2.27-2.51 (1H, m), 3.61-4.00 (2H, m), 4.43 and 4.44 (total 3H, each s), 5.38-5.46 (1H, m), 7.23 (2H, d, J = 8.6 Hz), 7.24-7.60 (2H, m), 8.11-8.19 (2H, m), 8.67-8.70 (1H, m), 8.77 (1H, brs), 9.46 (1H, d, J = 8.6 Hz).
ESI-MS (m/e): 482 (M+H).

Example 534

6-(1-acetyl pyrrolidin-2-yl)-5-((6-bromopyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-bromopyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.60-2.50 (7H, m), 3.60-3.95 (2H, m), 5.20-5.50 (1H, m), 6.80-8.40 (5H, m), 8.50-8.80 (2H, m), 9.50-9.70 (1H, m), 10.40-11.10 (1H, m).
ESI-MS (m/e): 479,481 (M+H).

Example 535

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol enantiomer A and enantiomer B

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer B 10 mg obtained in Example 493 was optically resolved with column for optical resolution (CHIRALPAK AD 2 cmϕ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 40/60/0.1, flow rate: 10 ml/min), and enantiomer A (retention time : 10.5 min) and enantiomer B (retention time : 19.0 min) were respectively obtained as white solid.

Enantiomer A
ESI-MS (m/e): 495 (M+H).

Enantiomer B
ESI-MS (m/e): 495 (M+H).

Example 536

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.88 and 2.02 (total 3H, each s), 1.93-2.20 (3H, m), 2.28-2.50 (1H, m), 3.60-4.00 (2H, m), 4.47 and 4.48 (total 3H, each s), 5.32-5.42 (1H, m), 7.22-7.70 (4H, m), 7.95-8.02 (1H, m), 8.25-8.32 (2H, m), 8.61-8.64 (1H, m), 8.73 (1H, brs).

ESI-MS (m/e): 482 (M+H).

Example 537

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR(CD_3OD) δ : 1.91 and 2.16 (total 3H, each s), 2.00-2.20 (3H, m), 2.38-2.55 (1H, m), 3.63-4.01 (2H, m), 4.50 and 4.51 (total 3H, each s), 5.35-5.44 (1H, m), 7.33-7.60 (2H, m), 7.66-7.73 (1H, m), 8.27-8.34 (1H, m), 8.65-8.67 (1H, m), 8.71-8.73 (1H, m), 8.78-8.80 (1H, m), 9.48-9.50 (1H, m).

ESI-MS (m/e): 483 (M+H).

Example 538

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.91-2.20 (6H, m), 2.33-2.52 (1H, m), 3.60-4.00 (2H, m), 4.48-4.90 (3H, m), 5.37-5.44 (1H, m), 7.22-7.68 (4H, m), 7.97-8.04 (1H, m), 8.19-8.23 (1H, m), 8.25-8.31 (1H, m), 8.55-8.59 (1H, m), 8.74 (1H, brs).

ESI-MS (m/e): 482 (M+H).

Example 539

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-1H-tetrazol-1-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(5-methyl-1H-tetrazol-1-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR(CD_3OD) δ : 1.91 and 2.16 (total 3H, each s), 1.96-2.20 (3H, m), 2.33-2.54 (1H, m), 2.63 and 2.64 (total 3H, each s), 3.64-4.00 (2H, m), 5.38-5.43 (1H, m), 7.32-7.57 (4H, m), 7.61-7.68 (2H, m), 8.70-8.73 (1H, m), 8.78-8.80 (1H, m), 9.47-9.49 (1H, 1).

ESI-MS (m/e): 482 (M+H).

Example 540

6-(1-acetyl pyrrolidin-2-yl)-5-((6-[1H-pyrazol-1-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(1H-pyrazol-1-yl) pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.67-2.48 (7H, m), 3.50-3.92 (2H, m), 5.14-5.57 (1H, m), 6.41-6.50 (1H, m), 6-80-8.03 (7H, m), 8.17-8.67 (4H, m), 11.00-11.11.27 (1H, m).

ESI-MS (m/e): 466 (M+H).

Example 541

6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-((6-[1H-[1,2,4]-triazol-1-yl) pyridin-3-yl) oxy)-1H-benzimidazole

Using 6-(1H-[1,2,4]-triazol-1-yl) pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.62-2.45 (7H, m), 3.52-3.90 (2H, m), 5.20-5.55 (1H, m), 6.79-8.68 (10H, m), 9.02-9.13 (1H, m), 11.17-11.52 (1H, m).

ESI-MS (m/e): 467 (M+H).

Example 542

5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer A and enantiomer B

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole 59.0 mg obtained by the same processes as in Example 162 (Step 2)-(Step 7) was optically resolved with column for optical resolution (CHIRALPAK AD 2 cmϕ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: ethanol / 2-propanol / diethylamine 25/75/0.1, flow rate: 12-18 ml/min), and enantiomer A and enantiomer B were respectively obtained as pale yellow solid. (retention time : enantiomer A 13.5 min, enantiomer B 30.8 min, CHIRALPAK AD 4.6 mmϕ x 250 cmL (made by Daicel Chemicals

Co.), mobile phase: ethanol / 2-propanol / diethylamine 25/75/0.1, flow rate: 1 ml/min).

Example 543

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

To 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer A 24.7 mg obtained in Example 542 dissolved in chloroform 1 ml was added anhydrous acetic acid 0.006 ml, and the reaction liquor was stirred at room temperature for ten minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel$^{TM}60F_{254}$, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

^{1}H-NMR(CD_3OD) δ : 1.90-2.20 (6H, m), 2.24-2.49 (1H, m), 3.66-4.00 (2H, m), 5.37-5.46 (1H, m), 7.12-7.60 (5H, m), 7.94-8.04 (1H, m), 8.04-8.20 (2H, m), 8.29 (1H, t, J = 8.2 Hz), 8.68-8.78 (1H, m).

ESI-MS (m/e): 481 (M+H).

Example 544

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

To chloroform 1 ml solution of 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer B 30.9 mg obtained in Example 542 was added acetic anhydride 0.007 ml, and thereafter, the reaction liquor was stirred at room temperature for 10 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel$^{TM}60F_{254}$, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

ESI-MS (m/e): 481 (M+H).

Example 545

5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A, B, C and D

Using 5-methyl dihydrofuran-2(3H)-one, 4-component mixture of the title compound was obtained by a process same as Example 485, process based on this or combining these with the normal method. The obtained 4-component mixture 15 mg was column for optically resolution (CHIRAL-CEL OD-H 2 cmϕ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane/ ethanol diethylamine = 80/20/0.1), and enantiomer A (retention time : 13.67 min), enantiomer B

(retention time : 15.24 min), enantiomer C (retention time : 18.96 min) and enantiomer D (retention time : 22.90 min) were respectively obtained as pale yellow solid.

Enantiomer A
^{1}H-NMR ($CDCl_3$) δ : 1.23-1.38 (3H, m), 1.50-2.57 (7H, m), 3.04 and 3.08 (3H, s), 4.24-4.60 (1H, m), 5.18-5.43 (1H, m), 6.92-7.83 (5H, m), 7.83-7.98 (3H, m), 8.34-8.43 (1H, m), 8.60-8.67 (1H, m), 10.84-11.33 (1H, m).
ESI-MS (m/e): 491 (M+H).

Enantiomer B
^{1}H-NMR ($CDCl_3$) δ : 1.22-2.20 (9H, m), 2.23-2.45(1H, m), 3.04 and 3.08 (3H, s), 4.10-4.22 (1H, m), 5.09-5.23 (1H, m), 7.04-7.70 (5H, m), 7.83-7.97 (3H, m), 8.34-8.48 (1H, m), 8.61-8.69 (1H, m), 10.73-11.16 (1H, m).
ESI-MS (m/e): 491 (M+H).

Enantiomer C
ESI-MS (m/e): 491 (M+H).

Enantiomer D.
ESI-MS (m/e): 491 (M+H).

Example 546

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 526, a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR(CD_3OD) δ : 1.88-2.20 (6H, m), 2.21-2..31 (1H, m), 3.61-4.00 (2H, m), 4.46 and 4.47 (total 3H, each s), 5.34-5.44 (1H, m), 7.22-7.71 (3H, m), 8.18-8.25 (1H, m), 8.50-8.60 (1H, m), 8.65-8.70 (1H, m), 8.72-8.80 (1H, m), 9.44-9.47 (1H, m).
ESI-MS (m/e): 483 (M+H).

Example 547

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-(methoxymethyl)-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-(methoxymethyl)-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.90-2.20 (6H, m), 2.22-2.71 (1H, m), 3.53 (3H, s), 5.38-5.46 (1H, m), 5.96 and 5.97 (total 3H, each s), 7.20-7.56 (5H, m), 7.95-8.03 (1H, m), 8.17-8.22 (2H, m), 8.29 (1H, t, J = 8.0 Hz), 8.73-8.79 (1H, m).
ESI-MS (m/e): 511 (M+H).

Example 548

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(methoxymethyl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.60-2.43 (7H, m), 3.34-3.91 (5H, m), 4.45-4.59 (2H, m), 5.20-5.52 (1H, m), 6.86-7.67 (5H, m), 7.80-7.90 (1H, m), 8.29-8.48 (2H, m), 8.55-8.67 (1H, m), 10.87-11.27 (1H, m).
ESI-MS (m/e): 444 (M+H).

Example 549

2-(2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure using 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained by the same processes as in Example 162 (Step 2)-(Step 7).
^{1}H-NMR(CD_3OD) δ : 1.94-2.16 (3H, m), 2.23-2.48 (1H, m), 3.57-4.34 (4H, m), 4.43 and 4.44 (total 3H, each s), 5.27-5.52 (1H, m), 7.17-7.57 (5H, m), 7.94-8.04 (1H, m), 8.09-8.20 (2H, m), 8.24-8.32 (1H, m), 8.69-8.81 (1H, m).
ESI-MS (m/e): 497 (M+H).

Example 550

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide diastereomer B obtained in Example 493 and 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure..
^{1}H-NMR ($CDCl_3$) δ : 1.82-2.43 (5H, m), 2.68 and 2.70 (3H, s), 3.64-4.40 (2H, m), 5.19-5.40 (1H, m), 5.42-5.64 (1H, m), 7.02-7.79 (4H, m), 7.80-7.92 (1H, m), 8.00-8.12 (1H, m), 8.35-8.42 (1H,

m), 8.60-8.75 (2H, m), 10.50-10.68 (1H, m).
ESI-MS (m/e): 500 (M+H).

Example 551

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-ethyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-ethyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR(CD_3OD) δ : 1.68 (3H, t, J = 7.2 Hz), 1.90 and 2.13 (total 3H, each s), 1.97-2.20 (3H, m), 2.29-2.53 (1H, m), 3.62-4.00 (2H, m), 4.73-7.79 (2H, m), 5.37-5.47 (1H, m), 7.19-7.60 (5H, m), 7.93-8.03 (1H, m), 8.10-8.20 (2H, m), 8.23-8.33 (1H, m), 8.74 (1H, brs)
ESI-MS (m/e): 495 (M+H).

Example 552

2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 184, a process based on this or a combination of these with a normal procedure using 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained by the same process as in Example 162 (Step 2)-(Step 7).
^{1}H-NMR(CD_3OD) δ : 1.97-2.10 (3H, m), 2.28-2.41 (1H, m), 3.52-3.63 (1H, m), 3.74-3.62 (1H, m), 5.26-5.41 (1H, m), 7.10-7.33 (1H, m), 7.23 (2H, d, J = 8.8 Hz), 7.44-7.61 (2H, m), 7.95-7.99 (1H, m), 8.12 (2H, d, J = 8.8 Hz), 8.27 (1H, d, J = 8.2 Hz), 8.72-8.73 (1H, m).
ESI-MS (m/e): 482 (M+H).

Example 553

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 550, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR(CD_3OD) δ : 1.83-2.17 (total 3H, each s), 2.10-2.40 (2H, m), 3.62-4.21 (2H, m), 4.41 and 4.42 (total 3H, each s), 5.23-5.43 (1H, m), 5.46-5.73 (1H, m), 7.10-7.65 (5H, m), 7.94-8.02 (1H, m), 8.03-8.17 (2H, m), 8.27 (1H, t, J = 8.8 Hz), 8.72 (1H, brs).
ESI-MS (m/e): 499 (M+H).

Example 554

5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridine-2-one enantiomer A and enantiomer B

Using 5'-hydroxy-2H-1,2'-bipyridin-2-one,

5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one 15.0 mg obtained by the same process as in Example 162 (Step 2)-(Step 7) was optically resolved with column for optical resolution (CHIRALPAK AD 2 cmϕ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: 2-propanol, flow rate: 10 ml/min), and enantiomer A (retention time: 23.6 min), enantiomer B (retention time: 50.7 min) were respectively obtained as pale yellow solid.

Example 555

5'-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer A

To 5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer A 6.5mg obtained in Example 554 dissolved in chloroform 1 ml was added acetic anhydride 0.003 ml, and thereafter the reaction liquor was stirred at room temperature for 30 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

^{1}H-NMR(CD_3OD) δ : 1.91 and 2.16 (total 3H, each s), 1.94-2.20 (3H, m), 2.32-2.52 (1H, m), 3.63-3.98 (2H, m), 5.38-5.44 (1H, m), 6.49-6.54 (1H, m), 6.63-6.68 (1H, m), 7.23-7.58 (3H, m), 7.60-7.67 (2H, m), 7.77 (1H, dd, J = 8.8, 15.8 Hz), 7.87-7.93 (1H, m), 7.95-8.01 (1H, m), 8.27-8.31 (1H, m), 8.41 (1H, d, J = 2.9 Hz), 8.73 (1H, t, J = 4.7 Hz)

ESI-MS (m/e): 493 (M+H).

Example 556

5'-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer B

To chloroform 1 ml solution of 5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer B 5.8 mg obtained in Example 554, acetic anhydride 0.003 ml was added, and thereafter the reaction liquor was stirred at room temperature for 30 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

ESI-MS (m/e): 493 (M+H).

Example 557

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using

cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.80-2.84 (2H, m), 1.94 and 2.25 (total 3H, each s), 3.90-4.30 (2H, m), 4.43 (3H, s), 5.28-5.50 (1H, .m), 5.51-5.59 (1H, m), 7.18-7.64 (5H, m), 7.94-8.01 (1H, m), 8.12-8.18 (2H, m), 8.25-8.29 (1H, m), 8.70-8.77 (1H, m).

ESI-MS (m/e): 499 (M+H).

Example 558

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one, the title compound was obtained as yellow oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.20-2.50 (7H, m), 3.50-4.00 (2H, m), 3.90-4.25 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (7H, m), 7.80-8.00 (1H, m), 8.25-8.50 (1H, m), 8.50-8.80 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 484 (M+H).

Example 559

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1-72-2.59 (10H, m), 3.53-3.90 (2H, m), 5.20-5.55 (1H, m), 6.81-7.66 (5H, m), 7.78-7.92 (1H, m), 8.28-8.43 (2H, m), 8.55-8.66 (1H, m), 11.07-11.55 (1H, m).

ESI-MS (m/e): 414 (M+H).

Example 560

6-(1-acetyl pyrrolidin-2-yl)-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-pyrazin-2-yl pyridin-3-ol, the title compound was obtained as a yellow oily substance by the same process as in Example 483, a process based on this or a combination of these with a

normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 0.80-2.40 (7H, m), 3.60-3.90 (2H, m), 5.20-5.60 (1H, m), 7.00-7.80 (4H, m), 7.80-8.00 (1H, m), 8.30-8.50 (2H, m), 8.50-8.80 (4H, m), 9.50-9.70 (1H, m), 10.40-10.80 (1H, m).

ESI-MS (m/e): 478 (M+H).

Example 561

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4 -acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 2'-fluorobiphenyl-4-ol, the title compound was obtained as a yellow oily substance in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 0.80-2.80 (6H, m), 3.80-4.40 (2H, m), 5.05-5.50 (1H, m), 7.00-7.70 (11H, m), 7.75-7.95 (1H, m), 8.30-8.50 (1H, m), 8.50-8.75 (1H, m), 10.60-10.80 (1H, m).

ESI-MS (m/e): 511 (M+H).

Example 562

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-(4-pyrazin-2-yl phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2 -carbonyl)-amino)-phenyl-4-acetoxy -pyrrolidine obtained in Example 325 (Step 5) and 4-pyrazin-2-yl phenol, the title compound was obtained as yellow oily substance in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.20-2.80 (6H, m), 3.80-4.40 (2H, m), 5.20-5.50 (1H, m), 7.00-7.70 (5H, m), 7.80-7:95 (1H, m), 7.95-8.20 (2H, m), 8.30-8.50 (2H, m), 8.50-8.80 (2H, m), 8.95-9.20 (1H, m), 10.60-10.80 (1H, m).

ESI-MS(m/e): 495 (M+H).

Example 563

N-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methyl) acetamide

Using N-((5-hydroxypyridin-2-yl) methyl) acetamide, the title compound was obtained as oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.83-2.47 (10H, m), 3.54-3.90 (2H, m), 4.48-4.59 (2H, m), 5.21-5.50 (1H, m), 6.66-7.69 (6H, m), 7.79-7.91 (1H, m), 8.30-8.44 (2H, m), 8.54-8.69 (1H, m), 10.96-11.29 (1H, m).

ESI-MS (m/e): 471 (M+H).

Example 564

6-(1-acetyl pyrrolidin-2-yl)-5-((6-fluoropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-fluoropyridin-3-ol, the title compound was obtained as yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.40-2.50 (7H, m), 3.50-4.00 (2H, m), 5.00-5.60 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.00-8.15 (1H, m), 8.25-8.50 (1H, m), 8.50-8.70 (1H, m), 10.60-10.80 (1H, m).

ESI-MS(m/e): 418[M+H].

Example 565

Cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

Step 1

Synthesis of cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H -benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

In accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure, the title compound was obtained using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 6-cyano-pyridin-3-ol.

Step 2

Production of cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

Using cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol -5-yl)-pyrrolidin-1-yl)-ethanone of racemic body obtained in (Step 1), the title compound was respectively obtained by the same process as in Example 333, a process based on this or a combination of these with a normal procedure.

Enantiomer A.

^{1}H-NMR(CD_3OD) δ : 1.91 (3H x 1/2, s), 2.22 (3H x 1/2, s), 2.32-2.67 (2H, m), 3.95-4.30 (2H, m), 5.27-5.47 (2H, m), 7.35-7.64 (3H, m), 7.85-7.92 (1H, m), 7.97-7.99 (1H, m), 8.29 (1H, t, J = 7.6 Hz), 8.60 (1H, d, J = 3.1 Hz), 8.74 (1H, s).

ESI-MS (m/e): 443 (M+H).

Enantiomer B.
ESI-MS (m/e): 443 (M+H).

Example 566

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

Step 1

Synthesis of N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide diastereomer B300 mg obtained in Example 493 was optically resolved with column for optical resolution (CHIRAL CEL OD 2 cmϕ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 50/50/0.1, flow rate: 10 ml/min), and enantiomer A and enantiomer were respectively obtained as yellow solid.

Step 2

Production of 6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer A and 2'-fluorobiphenyl-4-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.82-2.43 (5H, m), 3.63-4.36 (2H, m), 5.25-5.70 (2H, m), 7.07-7.58 (11H, m), 7.74-7.90 (1H, m), 8.35-8.43 (1H, m), 8.58-8.68 (1H, m), 10.37-10.60 (1H, m).
ESI-MS (m/e): 511 (M+H).

Example 567

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 566 (Step 1), the title compound was obtained in accordance with Example 566 (Step 2), a process based on this or a combination of these with a conventional procedure.
ESI-MS(m/e): 511 (M+H).

Example 568

Cis-1-(4-fluoro-2-(6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-ethanesulfonyl-phenol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR(CD_3OD) δ : 1.90 (3H x 0.5, s), 2.22 (3H x 0.5, s), 2.25-2.75 (2H, m), 3.88-4.39 (2H, m), 5.24-5.48 (2H, m), 7.23-7.75 (5H, m), 7.90-8.02 (3H, m), 8.27-8.30 (1H, m), 8.73-8.75 (1H, m).
ESI-MS (m/e): 509 (M+H).

Example 569

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidine-2-one enantiomer A

Step 1

Synthesis of t-butyl 2-(2-fluoro-4-((pyrazine-2-ylcarbonyl) amino) phenyl) pyrrolidine-1-carboxylate

In 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 3 g obtained in Example 338 (Step 2) dissolved in pyridine 5 ml were added successively pyrazine-2-carboxylic acid 1.5 g, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 3.1 g, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform / methanol = 50/1) and the title compound was obtained as a yellow oily substance.

Step 2

Synthesis of N-(3-fluoro-4-pyrrolidin-2-yl phenyl) pyrazine-2-carboxamide dihydrochloride

To methanol 50 ml solution of t-butyl 2-(2-fluoro-4-((pyrazin-2-yl carbonyl) amino) phenyl) pyrrolidine-1-carboxylate 4.4 g was added 4 N hydrochloric acid-dioxane solution 50 ml, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow solid

Step 3

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide

To N-(3-fluoro-4-pyrrolidin-2-yl phenyl) pyrazine-2-carboxamide dihydrochloride 4.3 g dissolved in pyridine 50 ml solution, acetic anhydride 1.5 ml was added, and the reaction liquor was stirred at room temperature for 20 minutes. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter

dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 50/1) and the title compound was obtained as a yellow solid

Step 4

Synthesis of N-(4-[1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide

Fuming nitric acid 40 ml was added to N-(4-(1-acetyl pyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide 3.9 g under ice cooling, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was diluted with iced water, and it was made basic with saturated aqueous sodium bicarbonate, thereafter, extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform / methanol = 50/1) and the title compound was obtained as a yellow oily substance.

Step 5

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide 500 mg was optically resolved with column for optical resolution (CHIRALPAK OD 2 cmϕ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / 2-propanol 1/1, flow rate: 15 ml/min), and enantiomer A (retention time: 18 min), enantiomer B (retention time: 25 min) were respectively obtained as pale yellow oily substance.

Step 6

Production of 3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidine-2-one enantiomer A

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one and N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer A, the title compound, one of chiral body was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.00-2.40 (7H, m), 3.50-3,90(2H, m), 3.90-4.20 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (6H, m), 8.50-8.75 (2H, m), 9.50-9.70 (1H, m), 10.30-10.60 (1H, m).

ESI-MS (m/e): 485 (M+H).

Example 570

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one enantiomer B

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one and N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer B obtained in Example 569 (step 5), the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

ESI-MS (m/e): 485 (M+H).

Example 571

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(cyclopropyl sulfonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(cyclopropyl sulfonyl) phenol, the title compound was obtained as slight yellow solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 0.90-1.20 (2H, m), 1.20-1.40 (3H, m), 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 5.05-5.50 (1H, m), 7.00-8.20 (8H, m), 8.30-8.50 (1H, m), 8.55-8.80 (1H, m), 10.70-11.20 (1H, m).

ESI-MS(m/e): 503 (M+H).

Example 572

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methanesulfonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(ethanesulfonyl) phenol, the title compound was obtained as a white solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.20-1.40 (3H, m), 1.60-2.50 (7H, m), 3.00-3.20 (2H, m), 3.50-4.00 (2H, m), 5.10-5.50 (1H, m), 6.90-7.80 (5H, m), 7.80-8.00 (3H, m), 8.30-8.50 (1H, m), 8.50-8.75 (1H, m), 10.60-11.20 (1H, m).

ESI-MS (m/e): 491 (M+H).

Example 573

Cis-1-(4-fluoro-2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.20-1.40 (3H, m), 1.90-2.30 (3H, m), 2.00-2.80 (2H, m), 3.20-3.50 (2H, m), 3.84-4.25 (2H, m), 5.27-5.45 (2H, m), 7.40-7.80 (4H, m), 8.00-8.20 (2H, m), 8.24-8.40 (1H,

m), 8.66 (1H, s), 8.80 (1H, brs).
ESI-MS (m/e): 510 (M+H).

Example 574

Cis-1-(4-fluoro-2-(6-(6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR(CD_3OD) δ : 1.90-2.30 (3H, m), 2.00-2.80 (2H, m), 2.75 (3H, s), 3.84-4.40 (2H, m), 5.30-5.45 (2H, m), 7.25-7.80 (4H, m),-7.90-8.40 (3H, m), 8.55-8.68 (1H, m), 8.75 (1H, s).
ESI-MS (m/e): 500 (M+H).

Example 575

5-((6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridine-2-carbonitrile

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 566 (Step 1) and 5-hydroxypyridine-2-carbonitrile, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.54-2.45 (5H, m), 3.61-4.34 (2H, m), 5.09-5.54 (2H, m), 7.01-7.95 (6H, m), 8.34-8.47 (1H, m), 8.54-8.73 (2H, m), 10.66-10.79 (1H, m).
ESI-MS (m/e): 443 (M+H).

Example 576

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.54-2.45 (5H, m), 3.61-4.34 (2H, m), 5.09-5.54 (2H, m), 7.01-7.95 (6H, m), 8.34-8.47 (1H, m), 8.54-8.73 (2H, m), 10.66-10.79 (1H, m).
ESI-MS (m/e): 443 (M+H).

Example 577

6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-1H-benzimidazole

Using 6-pyrazin-2-yl pyridin-3-ol, the title compound was obtained as a straw-coloured oily

substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.05-2.50 (7H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 7.00-7.80 (3H, m), 8.20-8.45 (1H, m), 8.45-8.80 (5H, m), 9.50-9.70 (2H, m), 10.40-11.30 (1H, m).

ESI-MS (m/e): 479 (M+H).

Example 578

6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridin-3-ol and N-(4-(1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide obtained in Example 545, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.20-2.30 (7H, m), 2.30-2.70 (6H, m), 4.05-4.60 (1H, m), 5.20-5.60 (1H, m), 6.80-7.50 (4H, m), 7.70-7.90 (1H, m), 8.15-8.20 (1H, m), 8.25-8.40 (2H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 428 (M+H).

Example 579

6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 578, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.20-2.60 (10H, m), 4.05-4.65 (1H, m), 5.10-5.50 (1H, m), 6.80-7.70 (4H, m), 7.80-8.10 (2H, m), 8.15-8.50 (2H, m), 8.60-8.80 (1H, m), 10.80-11.30 (1H, m).

ESI-MS (m/e): 448 (M+H).

Example 580

2-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl sulphanyl) ethanol

To N,N-dimethylformamide 1 ml solution of 6-(1-acetyl pyrrolidin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole 20 mg obtained in Example 504 were added successively 2-mercaptoethanol 20 mg and potassium carbonate 10 mg, and the reaction liquor was stirred at 120°C for five hours. After cooling, the reaction liquor was diluted using saturated aqueous sodium bicarbonate, extracted with chloroform, and the organic layer was dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was refined by preparative thin layer

chromatography (Kieselgel™60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound was obtained as a white solid

^{1}H-NMR ($CDCl_3$) δ : 1.10-2.50 (7H, m), 3.20-3.40 (2H, m), 3.50-4.00 (4H, m), 5.20-5.50 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.10-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-10.80 (1H, m).

ESI-MS (m/e): 476 (M+H).

Example 581

3-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl sulphanyl) propane-1-ol

Using 3-mercapto propane-1-ol, the title compound was obtained as a white solid by the same process as in Example 580, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.50 (7H, m), 3.20-3.40 (2H, m), 3.50-4.40 (6H, m), 5.20-5.60 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.20-8.50 (2H, m), 8.50-8.70 (1H, m), 10.80-11.20 (1H, 1).

ESI-MS (m/e): 490 (M+H).

Example 582

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyridin-2-yl)-5-(4-methanesulphonyl-phenoxy) -1H-benzimidazole

Using 5-methyl picolinic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR(CD_3OD) δ : 1.86 and 2.10 (total 3H, each s), 1.92-2.43 (4H, m), 2.65 and 2.66 (total 3H, each s), 3.14 and 3.16 (total 3H, each s), 3.62-3.96 (2H, m), 5.25-5.32 (1H, m), 7.23 and 7.25 (total 2H, each d, J = 8.8 Hz), 7.20-7.58 (3H, m), 7.95 and 7.99 (total 2H, each d, J = 8.8 Hz), 8.38-8.42 (1H, m), 9.12-9.16 (1H, 1).

ESI-MS (m/e): 491 (M+H).

Example 583

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyrazine-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 5-methylpyrazine-2-carboxylic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR(CD_3OD) δ : 1.87-2.45 (7H, m), 2.66 and 2.67 (total 3H, each s), 3.14 and 3.16 (total 3H, each s), 3.63-4.00 (2H, m), 5.26-5.34 (1H, m), 7.20-7.61 (4H, m), 7.96 and 7.99 (total 2H, each d,

J = 8.8 Hz), 8.69 (1H, s), 9.32 and 9.34 (total 1H, each s).
ESI-MS (m/e): 492 (M+H).

Example 584

1-(4-((6-(1-acetyl-3-fluoropyridin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone

Using 1-(4-hydroxyphenyl) ethanone, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.62-2.60 (8H, m), 3.60-3.98, 4.04-4.33 (total 2H, each m), 5.11-5.56 (2H, m), 7.00-8.02 (8H, m), 8.33-8.48 (1H, m), 8.57-8.71 (1H, m), 10.76-11.09 (1H, m).
ESI-MS (m/e): 459 (M+H).

Example 585

6-(1-acetyl-3-fluoropyridin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.54-2.45 (5H, m), 3.60-4.35 (2H, m), 5.20-5.60 (2H, m), 6.90-7.00, 7.21-7.43, 7.60-7.93 (total 6H, eachm), 8.22-8.45 (2H, m), 8.58-8.70 (1H, m), 10.63-10.90 (1H, m).
ESI-MS (m/e): 452 (M+H).

Example 586

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.60-2.47 (7H, m), 2.57-2.73 (3H, m), 3.57-3.93 (2H, m), 5.21-5.48 (1H, m), 7.00-7.76 (3H, m), 7.96-8.14 (1H, m), 8.52-8.68 (3H, m), 9.54-9.65 (1H, m), 10.70-11.02, 11.53-10.66 (total 1H, each m).
ESI-MS (m/e): 483 (M+H).

Example 587

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(methanesulphonyl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(methanesulphonyl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.51-2.47 (7H, m), 3.14-3.27 (3H, m), 3.58-3.92 (2H, m), 5.14-5.40 (1H, m), 7.03-7.79 (4H, m), 7.95-8.11 (1H, m), 8.48-8.71 (2H, m), 9.56-9.66 (1H, m), 10.65-10.194, 11.34-11.49 (total 1H, each m).

ESI-MS (m/e): 479 (M+H).

Example 588

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone

Using 1-(4-hydroxyphenyl) ethanone, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.53-2.61 (10H, m), 3.51-3.93 (2H, m), 5.14-5.47 (1H, m), 6.95-7.74 (4H, m), 7.88-8.02 (2H, m), 8.53-8.68 (2H, m), 9.54-9.66 (1H, m), 10.60-10.88, 11.43-11.54 (total 1H, each m)

ESI-MS(m/e): 442 (M+H).

Example 589

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(difluoromethoxy) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(difluoromethoxy) pyridine-3-ol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR(CD_3OD) δ : 1.92 and 2.18 (total 3H, each s), 1.98-2.57 (4H, m), 3.65-4.00 (2H, m), 5.41-5,48(1H, m), 7.03 and 7.07 (total 1H, each d, J = 8.8 Hz), 7.00-7.72 (5H, m), 7.94-8.00 (1H, m), 8.08 (1H, s), 8.25 (1H, t, J = 7.4 Hz), 8.73 (1H, s).

ESI-MS (m/e): 466 (M+H).

Example 590

6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-5-(4-pyrazin-2-yl phenoxy)-1H-benzimidazole

Using 4-pyrazin-2-yl phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR($CDCl_3$) δ : 1.10-2.60 (7H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.70-7.80 (4H, m), 7.90-8.20 (2H, m), 8.50-8.80 (4H, m), 8.95-9.20 (1H, m), 9.50-9.75 (1H, m), 10.60-11.40 (1H, m).

ESI-MS (m/e): 478 (M+H).

Example 591

4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) benzonitrile

Using 4-cyanophenol, the title compound was obtained as a yellow oily substance by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.50-2.50 (7H, m), 3.50-3.90 (2H, m), 5.05-5.50 (1H, m), 6.65-7.80 (6H, m), 8.50-8.80 (2H, m), 9.50-9.70 (1H, m), 10.40-11.20 (1H, m).

ESI-MS (m/e): 425 (M+H).

Example 592

Methyl 4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) benzoate

Using methyl 4-hydroxybenzoate, the title compound was obtained as a yellow oily substance by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.60-2.50 (7H, m), 3.50-4.00 (5H, m), 5.10-5.60 (1H, m), 6.70-7.80 (4H, m), 7.90-8.20 (2H, m), 8.50-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.60 (1H, m).

ESI-MS (m/e): 458 (M+H).

Example 593

2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide

Using 2'-fluorobiphenyl-4-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 182, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR (DMSO-d_6) δ : 1.60-2.60 (4H, m), 3.20-4.20 (2H, m), 5.10-5.30 (1H, m), 5.60-5.90 (2H, m), 6.90-7.70 (11H, m), 7.90-8.10 (1H, m), 8.20-8.40 (1H, m), 8.60-8.80 (1H, m).

ESI-MS (m/e): 494 (M+H).

Example 594

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure..

^{1}H-NMR ($CDCl_3$) δ : 1.60-2-80 (10H, m), 3.50-4.00 (2H, m), 5.15-5.60 (1H, m), 6.70-7.80 (5H, m), 7.90-8.20 (2H, m), 8.50-8.70 (1H, m), 9.50-9.70 (1H, m), 10.60-11.50 (1H, m).

ESI-MS (m/e): 482 (M+H).

Example 595

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Step 1

Synthesis of 2-fluoro-N-methoxy-N-methylbenzamide

To 2-fluoro-4-nitrobenzoic acid 10 g suspended in pyridine 80 ml were added N-methoxy-N-methylamine hydrochloride 5.79 g and 1-ethyl-3-(3'-dimethylaminopropyl) -carbodiimide hydrochloride 12.4 g, and the reaction liquor was stirred overnight at room temperature. Pyridine was eliminated by distillation under reduced pressure, and thereafter, water was added. The obtained precipitate was recovered by filtration and, by washing with water and drying, the title compound was obtained as a straw-coloured solid.

Step 2

Synthesis of 4-amino-2-fluoro-N-methoxy-N-methylbenzamide

To 2-fluoro-N-methoxy-N-methylbenzamide 10.84 g suspended in methanol 60 ml and water 30 ml, ammonium chloride 15.2 g and iron powder 8 g were added, and the reaction liquor was heated under reflux for three hours. The reaction liquor was filtered using celite, and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained residue was diluted with ethyl acetate and was washed using water and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/2) and the title compound was obtained as brown oily substance.

Step 3

Synthesis of N-(3-fluoro-4-((N-methoxy-N-methylamino) carbonyl) phenyl) pyrazine-2-carboxamide

To 4-amino-2-fluoro-N-methoxy-N-methylbenzamide 3.7 g dissolved in pyridine 20 ml were added pyrazine-2-carboxylic acid 2.56 g and 1-ethyl-3-(3'-dimethylaminopropyl)- carbodiimide hydrochloride 4.66 g, and the reaction liquor was stirred at room temperature for one hour. Pyridine was eliminated by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed using water and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and, by washing the obtained solid with mixed solvent of ethyl acetate and hexane, the title compound was obtained as a straw-coloured solid.

Step 4

Synthesis of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-2-pentinoyl)-3-fluorophenyl) pyrazine-2-carboxamide

To (3R)-3-(tert-butyl (dimethyl) silyl) oxy-1-butyne 4.92 g dissolved in tetrahydrofuran 80 ml was added n-butyllithium (2.46M hexane solution) 10.8 ml at -78°C, and the reaction liquor was stirred at the same temperature for one hour. N-(3-fluoro-4-((N-methoxy-N -methylamino) carbonyl) phenyl) pyrazine-2-carboxamide 2.7 g dissolved in tetrahydrofuran 60 ml was added at -78°C, and the reaction liquor was warmed to room temperature, and thereafter, it was stirred for two hours. Water was added to the reaction liquid and the liquid extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/1), and the title compound was obtained as a yellow solid

Step 5

Synthesis of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-pentinoyl)-3-fluorophenyl) pyrazine-2-carboxamide

To solution of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-2-pentinoyl)-3-fluorophenyl) pyrazine-2-carboxamide in mixture of 513 mg ethanol 20 ml and tetrahydrofuran 5 ml was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred under a hydrogen atmosphere for one hour 30 minutes. After eliminating the catalyst by filtration, the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/1), and the title compound was obtained as a straw-coloured solid.

Step 6

Synthesis of N-(4-((4R)-1,4-dihydroxy pentyl)-3-fluorophenyl) pyrazine-2-carboxamide

To a solution of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-pentinoyl)-3-fluorophenyl) pyrazine-2-carboxamide 340 mg in mixture of tetrahydrofuran 5 ml and methanol 10 ml was added sodium borohydride 89 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was concentrated down by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed with saturated ammonium chloride aqueous solution, and thereafter was dried with anhydrous magnesium sulphate. By eliminating under reduced pressure the solvent, crude product was obtained. To tetrahydrofuran 6 ml solution of the obtained crude product, tetrabutyl ammonium fluoride (1M tetrahydrofuran solution) 1.18 ml was added under ice cooling, and the reaction liquor was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate) and the title compound was obtained as a straw-coloured solid.

Step 7

Synthesis of N-(4-((5S)-1-acetyl-5-methylpyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide

To N-(4-((4R)-1,4-dihydroxy pentyl)-3-fluorophenyl) pyrazine-2-carboxamide 147 mg suspended in chloroform 6 ml were added triethylamine 0.26 ml and methanesulphonyl chloride 0.11 ml, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was diluted with chloroform, washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. By eliminating the solvent by distillation under reduced pressure, crude product was obtained. To dimethylformamide 4 ml solution of the obtained crude product, sodium azide 30 mg was added under ice cooling, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with ethyl acetate, washed using water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. By eliminating the solvent under reduced pressure, crude product was obtained. To methanol 5 ml solution of the obtained crude product, copper sulfate pentahydrate 15 mg and sodium borohydride 52 mg were added, and the reaction liquor was stirred at room temperature for two hours. Sodium borohydride 35 mg was added, and the reaction liquor was stirred for 30 minutes. Further sodium borohydride 35 mg was added, and the reaction liquor was stirred for 30 minutes. The solvent was eliminated by distillation under reduced pressure and thereafter the residue was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. By eliminating the solvent by distillation under reduced pressure, crude product was obtained. Acetic anhydride 0.043 ml was added to chloroform 4 ml solution of the obtained crude product, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel$^{TM}60F_{254}$, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as straw-coloured oily substance.

Step 8

Synthesis of N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide

To N-(4-((5S)-1-acetyl-5-methylpyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide 59 mg, fuming nitric acid 1 ml was added at room temperature, and the reaction liquor was stirred at the same temperature for 30 minutes. The reaction liquor was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel$^{TM}60F_{254}$, Art5744 (Merck Co.), ethyl acetate), and obtained the title compound as straw-coloured oily substance. (Rf : trans body > cis body)

Step 9

Production of

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

To N-methylpyrrolidinone 1 ml solution of N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide 10.4 mg were added 4-methansulphonyl-phenyl 9.2 mg, cesium carbonate 26.2 mg, and the reaction liquor was stirred at 90°C for one hour. Tin chloride (II) dihydrate 60 mg was added, and the reaction liquor was stirred at 90°C for one hour and at 100°C for two hours. To the reaction liquor were added ethyl acetate and saturated aqueous sodium bicarbonate, and precipitate was eliminated by filtration, thereafter extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as straw-coloured oily substance.

^{1}H-NMR ($CDCl_3$) δ : 1.31 and 1.33 (total 3H, each d, J = 6.0 Hz), 1.55-2.60 (7H, m), 3.03-3.10 (3H, m), 4.25-4.62 (1H, m), 5.20-5.44 (1H, m), 7.01-7.68 (4H, .m), 7.85-7.97 (2H, m), 8.57-8.69 (2H, m), 9.56-9.63 (1H, m).

ESI-MS (m/e): 492 (M+H).

Example 596

N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethanamine

Using 2-methyl-2H-tetrazol-5-yl phenol, the title compound was obtained as a yellow oily substance by the same process as in Example 498 (Step 5)-(Step 8), a process based on these or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.80-2.50 (7H, m), 2.90-4.00 (4H, m), 4.30-4.50 (3H, m), 5.10-5.65 (1H, m), 7.10 (2H, m), 7.20-7.85 (3H, m), 7.80-7.95 (1H, m), 8.05-8.20 (2H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 5.10 (M+H).

Example 597

6-(1-acetyl pyrrolidin-2-yl)-5-((4'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4'-fluorophenyl-4-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.66-2.43 (7H, m), 3.44-3.92 (2H, m), 5.21-5.60 (1H, m), 6.80-7.67 (11H, m), 7.77-7.91 (1H, m), 8.30-8.43 (1H, m), 8.53-8.67 (1H, m), 10.89-11.43 (1H, m).
ESI-MS (m/e): 493 (M+H).

Example 598

6-(1-acetyl pyrrolidin-2-yl)-5-((3'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole
Using 3'-fluorophenyl-4-ol, the title compound was obtained as a straw-coloured solid.
^{1}H-NMR ($CDCl_3$) δ : 1.67-2.44 (7H, m), 3.44-3.92 (2H, m), 5.22-5.58 (1H, m), 6.92-7.68 (11H, m), 7.78-7.93 (1H, m), 8.33-8.45 (1H, m), 8.56-8.68 (1H, m), 10.88-11.38 (1H, m).
ESI-MS (m/e): 493 (M+H).

Example 599

2-(5-((6-cyanopyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide
Using 6-cyanopyridin-3-ol, the title compound was obtained as a white solid the same process as in Example 162 and Example 182, a process based on these or a combination of these with a normal procedure.
^{1}H-NMR(CD80D) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 3.40-3.60 (1H, m), 3.70-3.80 (1H, m), 4.80-5.30 (1H, m), 6.60-6.75 (2H, m), 7.20-7.70 (3H, m), 7.80-8.20 (3H, m), 8.20-8.30 (1H, m), 8.50-8.65 (1H, m), 8.70-8.80 (1H, m).
ESI-MS (m/e): 426 (M+H).

Example 600

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole
Using N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide obtained in Example 595 (Step 8) and 4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenol, the title compound was obtained as pale yellow solid the same process as in Example 595 (Step 9), a process based on this or a combination of these with a normal procedure.
^{1}H-NMR ($CDCl_3$) δ : 1.33 and 1.34 (total 3H, each d, J = 6.0 Hz), 1.55-2.60 (7H, m), 2.68 and 2.70 (total 3H, each s), 4.26-4.62 (1H, m), 5.28-5.49 (1H, m), 7.03-8.12 (4H, m), 8.40-8.69 (3H, m), 9.57-9.63 (1H, 1).
ESI-MS (m/e): 497 (M+H).

Example 601

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyrazine-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)-phenoxy)-1H-benzi

midazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol and 5-methylpyrazine-2-carboxylic acid, the title compound was obtained as pale yellow solid the same process as in Example 306, a process based on this or a combination of these with a normal procedure.

^{1}H-NMR(CD_3OD) δ : 1.88-2.48 (7H, m), 2.63 and 2.64 (total 3H, each s), 3.61-3.99 (2H, m), 4.41 and 4.42 (total 3H, each s), 5.37-5.4 (1H, m), 7.15-7.55 (2H, m), 7.17 (2H, d, J = 8.8 Hz), 8.08 and 8.11 (total 2H, each d, J = 8.8 Hz), 8.64 (1H, s), 9.27 and 9.29 (total 1H, each s).

ESI-MS (m/e): 496 (M+H).

Example 602

6-(1-acetyl-4-methylpyrrolidin-2-yl)-5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Step 1

Synthesis of N-(3-fluoro-4-(3-methyl-3-butenoyl) phenyl) pyridine-2-carboxamide

Using pyridine-2-carboxylic acid, (2-methyl-2-propen-1-yl) magnesium chloride (0.50M tetrahydrofuran solution) 9.89 ml was added under ice cooling to tetrahydrofuran 10 ml solution of N-(3-fluoro-4-((methoxy (methyl) amino) carbonyl) phenyl) pyridine-2-carboxamide 500 mg obtained in accordance with the same process as in Example 145 (Step 3), a process based on this or a combination of these with a conventional procedure. The reaction liquor was stirred under ice cooling for three hours, and thereafter the reaction liquor was discharged into water, and extraction was carried out with ethyl acetate and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 3/1) and the title compound was obtained.

Step 2

Synthesis of N-(3-fluoro-4-(1-hydroxy-3-methyl-3-buten-1-yl) phenyl) pyridine-2-carboxamide

To N-(3-fluoro-4-(3-methyl-3-butenoyl) phenyl) pyridine-2-carboxamide 280 mg dissolved in methanol 5 ml solution, sodium borohydride 88.8 mg was added. The reaction liquor was stirred at room temperature for three hours, and thereafter, it was discharged into saturated ammonium chloride aqueous solution, and extraction was carried out with ethyl acetate and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1) and the title compound was obtained.

Step 3

Synthesis of N-(4-(1,4-dihydroxy-3-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide

Borane-methyl sulphide complex (1M dichloromethane solution) 1.20 ml was added under ice cooling to cyclohexene 0.082 ml dissolved in tetrahydrofuran 5 ml solution. The reaction liquor was stirred under ice cooling for ten minutes, and thereafter, N-(3-fluoro-4-(1-hydroxy-3-methyl-3-buten-1-yl) phenyl) pyridine-2-carboxamide 301 mg dissolved in tetrahydrofuran 3 ml solution was added, and the reaction liquor was stirred at room temperature for one hour. 5N sodium hydroxide aqueous solution and 35 % hydrogen peroxide aqueous solution 0.50 ml were added successively to the reaction liquor and stirred at room temperature for ten minutes. The reaction liquor was discharged into saturated ammonium chloride aqueous solution and was extracted with acetic acid ethyl ester, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 9/1) and the title compound was obtained.

Step 4

Synthesis of N-(3-fluoro-4-(4-methylpyrrolidin-2-yl) phenyl) pyridine-2-carboxamide

To N-(4-(1,4-dihydroxy-3-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide 236 mg dissolved in chloroform 5 ml solution, were added under ice cooling successively triethylamine 0.62 ml and methane sulphonyl chloride 0.213 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was discharged into saturated aqueous sodium bicarbonate and was extracted with chloroform, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To dimethylformamide 3 ml solution of the obtained crude product, sodium azide 53.0 mg was added under ice cooling. The reaction liquor was stirred under ice cooling for 30 minutes and thereafter, stirred at room temperature for three hours. The reaction liquor was diluted with ethyl acetate and was washed using water, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To methanol 4 ml solution of the obtained crude product, copper sulfate pentahydrate 20 mg and sodium borohydride 168 mg were successively added. The reaction liquor was stirred at room temperature for four hours, and thereafter, it was discharged into saturated aqueous sodium bicarbonate, and it was extracted with chloroform, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To chloroform 3 ml solution of the obtained crude product, acetic anhydride 0.050 ml was added, and the reaction liquor was stirred at room temperature for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/3), and the title compound was thereby obtained.

Step 5

Synthesis of N-(4-(1-acetyl-4-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide

N-(3-fluoro-4-(4-methylpyrrolidin-2-yl) phenyl) pyridine-2-carboxamide 70.7 mg was dissolved in fuming nitric acid 1 ml, and the reaction liquor was stirred at room temperature for ten minutes. The reaction liquor was discharged into saturated aqueous sodium bicarbonate and was extracted with acetic acid ethyl ester, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2), and the title compound was obtained.

Step 6

Production of 6-(1-acetyl-4-methylpyrrolidin-2-yl)-5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

To 2 ml N-methyl-pyrrolidinone solution of N-(4-(1-acetyl-4-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide 15 mg were added successively 4-(methanesulphonyl) phenol 13.4 mg and cesium carbonate 44.9 mg, and the reaction liquor was stirred at 90°C for one hour. After the addition of tin chloride dihydrate 43.8 mg to the reaction liquor, it was warmed to 100°C and was stirred for two hours. The reaction liquor was dissolved in ethyl acetate, and thereafter, it was washed with saturated aqueous sodium bicarbonate, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel^{TM}60F_{254}, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 0.80-2.63 (9H, m), 3.00-4.40 (2H, m), 3.05 and 3.08 (total 3H, each s), 5.03-5.43 (1H, m), 7.00-7.73 (5H, m)7.83-7.98 (3H, m), 8.33-8.43 (1H, m), 8.62-8.70 (1H, m), 10.62-10.80 (1H, m).

ESI-MS (m/e): 491 (M+H).

Example 603

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide obtained in Example 595 (Step 8) and 6-(methoxymethyl) pyridin-3-ol, the title compound was obtained as pale yellow oily substance in accordance with Example 595 (Step 9), a process based on this or a combination of these with a conventional procedure.

^{1}H-NMR ($CDCl_3$) δ : 1.10-2.22 (10H, m), 3.48 and 3.50 (total 3H, each s), 4.26-4.62 (1H, m), 4.57 and 4.59 (total 2H, each s), 5.33-5.52 (1H, m), 7.20-7.50 (4H, m), 8.40-8.70 (3H, m), 9.57-9.63 (1H, m).

ESI-MS (m/e): 459 (M+H).

Reference Example 1

[1,2,4] thiadiazole-5-carboxylic acid

To thio oxamic acid ethyl ester 1 g dissolved in chloroform 10 ml was added N,N-dimethylformamide dimethylacetal 2 ml, and the reaction liquor was stirred at room temperature for four hours. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/2) and amidine body 1.1 g was obtained as red oily substance.

To amidine body 1.09 g and pyridine 0.95 ml dissolved in ethanol 18 ml was added hydroxylamine-O-sulfonic acid 721 mg dissolved in ethanol 20 ml, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed with saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1) and [1,2,4] thiadiazole-5-carboxylic acid ethyl ester was obtained as straw-coloured oily substance. To the obtained [1,2,4] thiadiazole-5-carboxylic acid ethyl ester 300 mg dissolved in methanol 8 ml solution, 1N sodium hydroxide aqueous solution 5.7 ml was added, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was concentrated down by distillation under reduced pressure, and thereafter the residue was neutralized using 2 N hydrochloric acid. The reaction liquor was concentrated down by distillation under reduced pressure, and thereafter the residue was washed with chloroform-methanol = 10/1, and the title compound was obtained as a white solid by eliminating the obtained organic layer under reduced pressure.

Reference Example 2

2-difluoromethoxy-pyridin-3-ol

To 3-benzyloxy-2-hydroxypyridine 2 g suspended in acetonitrile 40 ml were added sodium carbonate 2.1 g and difluoro fluorosulfonyl acetic acid 1.24 ml, and the reaction liquor was stirred at room temperature for one hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-4/1) and difluoromethoxy body was obtained as straw-coloured oily substance. To difluoromethoxy body 2.38 g dissolved in methanol 25 ml solution, 10 % palladium-carbon catalyst 500 mg was added, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for one hour. The catalyst

was eliminated by filtration by celite, and, by eliminating the solvent under reduced pressure, the title compound was obtained as light purple oily substance.

Reference Example 3

6-methanesulphonyl-pyridin-3-ol

In 3-bromo-6-methanesulphonyl-pyridine 4.72 g dissolved in dimethylsulfoxide 8 ml were added bis (pinacolate) diboron 6.6 g, potassium acetate 5.9 g and (1,1'-bis (diphenylphosphino) ferrocene) dichloroparadium (II) dichloromethan complex 980 mg, and the reaction liquor was stirred at 80°C for two hours. Acetic acid ethyl ester and water were added to the reaction liquor, insolubles substance were eliminated by filtration with celite and thereafter, the organic layer was separated. The organic layer was washed using water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. 5N sodium hydroxide aqueous solution 60 ml and 30 % hydrogen peroxide water 30 ml were added to tetrahydrofuran 200 ml solution of the obtained residue at 0°C, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with diethyl ether and thereafter washed using water. The aqueous layer was acidified with 5 N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. By washing the obtained residue with mixed solvent of chloroform and hexane, the title compound was obtained as a brown solid.

Reference Example 4

6-ethanesulfonyl-pyridin-3-ol

Using 3-chloro-6-ethane sulfonyl-pyridine, the title compound was obtained the same method as in Reference Example 3, process base on this or by combining these with the normal method.

Reference Example 5

(2R,4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide

Step 1

Synthesis of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester

To (2R,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 3.61 g dissolved in dimethylformamide 60 ml were added successively tert-butyl diphenyl silyl chloride 2.32 g and imidazole 2.32 g, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with ethyl acetate, washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure,

and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2) and the title compound was obtained.

Step 2

Synthesis of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

To (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2.62 g dissolved in pyridine 30 ml solution obtained in (Step 1) were added successively 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 1.50 g and O,N-dimethyl hydroxylamine hydrochloride 761 mg, and the reaction liquor was stirred overnight at room temperature. The solvent of the reaction liquor was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained.

Step 3

Synthesis of (2R,4R)-4-hydroxy-2-methoxy-methyl-carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester

To tetrahydrofuran 30 ml solution of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester 2.04 g obtained in (Step 2) was added tetrabutyl ammonium fluoride (1M tetrahydrofuran solution) 7.46 ml, and the reaction liquor was stirred at room temperature for 20 minutes. The solvent of the reaction liquor was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/3) and the title compound was obtained.

Step 4

Production of (2R,4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide

To ethanol 20 ml solution of (2R,4R)-4-hydroxy-2-methoxy-methyl-carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester 600 mg obtained in (Step 3) was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred overnight under a hydrogen atmosphere. The reaction liqour was stirred under hydrogen atmosphere over night. The catalyst was eliminated by filtration with celite, thereafter the solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

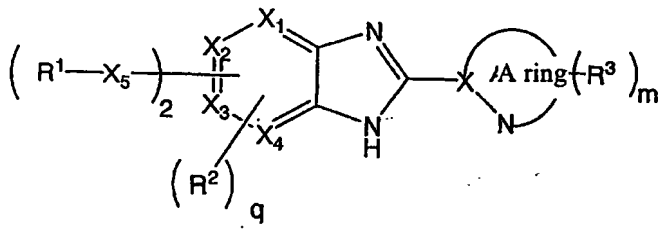
Possible Commercial Applications

The substituted benzimidazole derivatives in accordance with this invention and represented by aforesaid formula (I-O) demonstrate excellent glucokinase activity and therefore are useful in the

field of medicine, treatment and prevention of diabetes, diabetes complications and obesity.

Patent Claims

1. A compound represented by Formula (I-0), or pharmacologically acceptable salts thereof

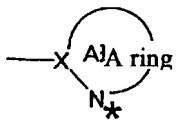


(I-0)

[wherein, X denotes a carbon atom or nitrogen atom,

X_1, X_2, X_3 and X_4 each independently denote carbon atom or nitrogen atom,

A ring denotes a 5-6 membered nitrogen containing heteroaromatic ring represented by formula (II)



(II)

which may containing 1-3 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (excluding the nitrogen atom represented by N* in formula II), or a bicyclic ring in which the said nitrogen containing heteroaromatic ring and phenyl or pyridyl are condensed,

R^1 denotes aryl or a 4-10 membered monocyclic or bicyclic heterorings containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said R^1 may be each independently substituted with 1to 3 R^4, moreover, when the said heteroring is an aliphatic heteroring, it may contain 1 or 2 double bonds),

R^2 each independently denote hydroxy, formyl, $-CH_{3-a}F_a$, $-OCH_{3-a}F_a$, amino, CN, halogen, C_{1-6} akyl or $(CH_2)_{1-4}OH$,

R^3 denotes $-C_{1-6}$ alkyl, $-(CH_2)_{1-6}-OH$, $-C(O)-OC_{1-6}$ alkyl, $-(CH_2)_{1-6}-OC_{1-6}$ alkyl, $-(CH_2)_{1-6}-NH_2$, cyano, $-C(O)-C_{1-6}$ alkyl, halogen, $-C_{2-6}$alkenyl, $-OC_{1-6}$alkyl, -COOH, -OH or oxo,

R^4 each independently,

$-C_{1-6}$ alkyl (the said alkyl may be substituted with the same or different 1 to 3 hydroxy, halogen, $-OC(O)-C_{1-6}$ alkyl (the said alkyl may be substituted with 1 to 3 halogen), or $-OC_{1-6}$ alkyl)

- C_{3-7} cycloalkyl,

- C_{2-6} alkenyl,

$-C(O)-N(R^{51})R^{52}$,

$-S(O)_2-N(R^{51})R^{52}$,

$-O-C_{1-6}$ alkyl (the said C_{1-6} alkyl may be substituted with halogen or $N(R^{51})R^{52}$),

$-S(O)_{0-2}-C_{1-6}$ alkyl,

$-C(O)-C_{1-6}$ alkyl (the said C_{1-6} alkyl may be substituted with halogen, amino, CN, hydroxy, -O-

C_{1-6} alkyl, $-CH_{3-a}F_a$, $-OC(O)-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)O-C_{1-6}$ alkyl, $-NH-C(O)O-C_{1-6}$ alkyl, phenyl, $-N(R^{51})R^{52}-NH-C(O)-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)-C(O)-C_{1-6}$ alkyl or $-NH-S(O)_{0-2}-C_{1-6}$ alkyl),

$-C(S)-C_{3-7}$ cycloalkyl,

$-C(S)-C_{1-6}$ alkyl,

$-C(O)-O-C_{1-6}$ alkyl,

$-(CH_2)_{0-4}-N(R^{53})-C(O)-R^{54}$,

$-N(R^{53})-C(O)-O-R^{54}$,

-C(O)-aryl (the said aryl may be substituted with halogen),

-C(O)-heteroaromatic ring,

-C(O)-aliphatic hetero ring,

hetero ring (the said hetero ring may be substituted with $-C_{1-6}$ alkyl (the said $-C_{1-6}$ alkyl may be substituted with halogen or $-O-C_{1-6}$ alkyl),

phenyl (the said phenyl may be substituted with halogen, $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl),

halogen, CN, formyl, COOH, amino, oxo, hydroxy, hydroxy amidino or nitro,

R^{51} and R^{52} each independently denote hydrogen atom, $-C_{1-6}$ alkyl,

or 4-7 membered hetero ring formed by linking nitrogen atom, R^{51} and R^{52} together,

R^{53} denotes a hydrogen atom or $-C_{1-6}$ alkyl,

R^{54} denotes $-C_{1-6}$ alkyl or,

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of R^{53} and R^{54}, and -N-C(O)- together or

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of R^{53} and R^{54}, and -N-C(O)-O- together (the said aliphatic hetero ring may be substituted with oxo, and moreover, the said aliphatic hetero ring may contain 1 or 2 double bonds in the ring),

X_5 denotes -O-, -S-, -S(O)-, $-S(O)_2-$, single bond or $-O-C_{1-6}$ -alkyl",

a denotes, each independently, an integer of 1, 2 or 3,

q denotes an integer of 0-2,

m denotes an integer of 0-2]

(wherein the following cases were excluded:

the case wherein one of X_5 is -O-, -S-, -S(O)- or $-S(O)_2-$, and the other X_5 is single bond, and also R^1 is aryl or nitrogen-containing aromatic heteroring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said aryl may be substituted with 1-3 R^4),

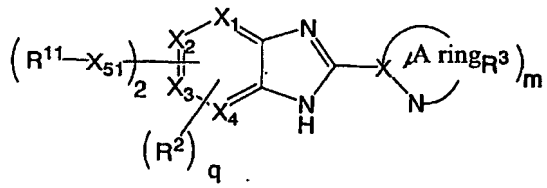
the case wherein both X^5 are single bonds, or

the case wherein both R^1 are aliphatic heteroring).

2. A compound in accordance with Claim 1 or pharmacologically acceptable salts thereof, wherein X_1 to X_4 are all carbon atoms.

3. A compound in accordance with Claim 1 or pharmacologically acceptable salts thereof, wherein X_5 is -O-, -S-, -S(O)-, -$S(O)_2$- or single bond.

4. A compound in accordance with Claim 1 represented by formula (I-1) or pharmacologically acceptable salts thereof



(I-1)

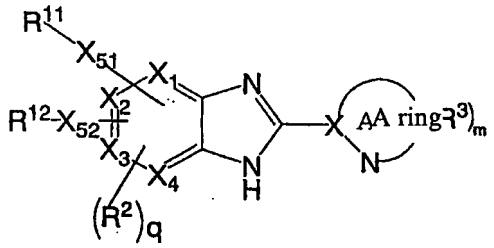
[in the formula, R^{11} denotes phenyl which may be substituted with 1-3 R^4 or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4), and aslo
X_{51} denotes -O-, -S-, -S(O)- or -$S(O)_2$-, and the other symbols are the same as above].

5. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein both R^{11} are phenyl which may be substituted with 1-3 R^4.

6 A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein both R^{11} are 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4).

7. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein one of the R^{11} is phenyl which may be substituted with 1-3 R^4 and also the other R^{11} is 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4).

8. A compound in accordance with Claim 1 represented by formula (I-2) or pharmacologically acceptable salts thereof



(I-2)

[in the formula, R^{11} denotes phenyl which may be substituted with 1-3 R^4 or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R^4),

R^{12} denotes 4 to 7-membered nitrogen-containing heteroring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said R^{12} may be substituted with 1-3 R^4, and moreover, when the said hetero ring is an aliphatic hetero ring, it may contain 1 or 2 double bonds),

X_{51} is -O-, -S-, -S(O)- or $-S(O)_2-$,

X_{52} is -O-, -S-, -S(O)-, $-S(O)_2-$ or single bond, and the other symbols are the same as above].

9. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein R^{12} is 4 to 7-membered nitrogen-containing saturated aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3 R^4. And also X_{52} is a single bond, or

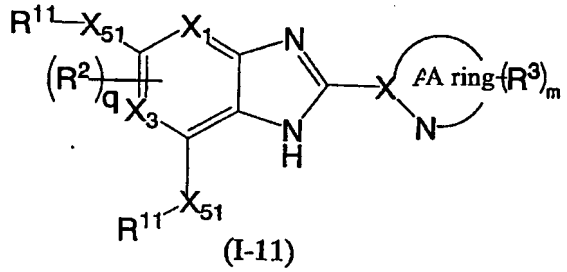
R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4. And also X_{52} is is -O-, -S-, -S(O)- or $-S(O)_2-$.

10. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein R^{12} is 4 to 7-membered nitrogen-containing saturated aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3 R^4. And also X_{52} is a single bond.

11. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4. And also X_{52} is -O-, -S-, -S(O)- or $-S(O)_2-$.

12. A compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2), R^{12} is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid R^4. And also X_{52} is -O-.

13. A compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-11)

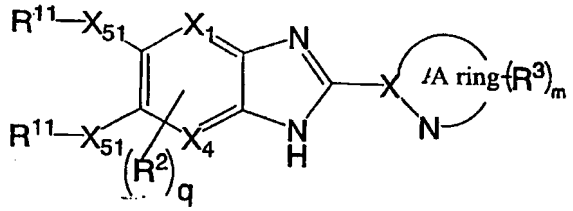


(I-11)

(each symbol is the same as above).

14. A compound in accordance with Claim 13 or pharmacologically acceptable salts thereof, wherein both X_{51} are -O-.

15. A compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-12)



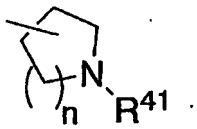
(I-12)

(each symbol is the same as above).

16. A compound in accordance with Claim 15 or pharmacologically acceptable salts thereof,

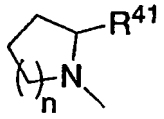
wherein both X_{51} are -O-.

17. A compound in accordance with Claim 10 or pharmacologically acceptable salts thereof, wherein R^{12} is formula (III-1)



(III-1)

or formula (III-2)



(III-2)

[wherein, n denotes an integer of 1-3, and R^{41} denotes the group same as the aforesaid R^4].

18. A compound in accordance with any one of Claims 1 to 17 or pharmacologically acceptable salts thereof, wherein the A ring is thiazolyl, imidazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, pyrazolyl or pyrimidinyl wll of which may be substituted with 1-3 of aforesaid R^4.

19. A compound or pharmacologically acceptable salts thereof, wherein the compound represented by formula (I-0) is

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole,

5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole,

5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazo

le,

5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2,6-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2-cyanopyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidaz

ole,
5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimid
azole,
5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-b
enzimidazole,
5-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-
1H-benzimidazole,
4-(2-fluoro-phenoxy)-2-(pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole,
4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimida
zole,
4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimida
zole,
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole
,
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole
,
4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1
H-benzimidazole,
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimi
dazole,
4-(2-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,
4-(2,3-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole
,
4-(2,5-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole
,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimid
azole,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzi
midazole,
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzi
midazole,
1-(2-(6-(5-bromo-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethano
ne,
1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-
1-yl)-ethanone,
1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethan
one,
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-et

hanone,

2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carbox amide,

2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrro lidin-1-yl)-ethanone,

1-(2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-et hanone,

2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidi n-1-yl)-ethanone,

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile,

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylamino-ethanone,

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidi n-1-yl)-ethanone,

N-(5-(6-[1-acetyl-pyrrolidin-2-yl]-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-aceta mide,

1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrroli din-1-yl)-ethanone,

N-(2-(2-[6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl]-pyrrolidin-1-yl)-2-oxo-ethyl)-acetamide,

6-(1-acetylpyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole • mono trifluoroacetate,

1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyridine-2(1H)-one,

6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,

(2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine,

6-(1-acetylpyrrolidin-2-yl)-5-((6-[[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(1-acetyl-3-fluoropyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-(6-(methoxymethylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,

2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol,

2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide,

5'-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one,

3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,

6-(1-acetylpyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,

6-(1-acetyl-3-fluoropyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,

3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,

6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone,

6-(1-acetylpyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,

6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,

N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanamine,

6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone,

1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone,

1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone, or

1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrrolidin-2-yl)-ethanone.

20. A medicinal composition comprising the following (1)-(3) to be used for therapy, prevention and/or delay of onset of type II diabetes mellitus;

(1) a compound in accordance with any one of Claims 1-19,

(2) a compound of 1 or 2 or more, selected from the group comprising following (a)-(h),

(a) other glucokinase activator,

(b) bis-guanide,

(c) PPAR agonist,

(d) insulin,

(e) somatostatin,

(f) α-glucosidase inhibitor,

(g) insulin, and

(h) DPF-IV (dipeptidyl peptidase IV) inhibitor

(3) a pharmacologically acceptable carrier.

21. A glucokinase activator containing as effective ingredient a compound in accordance with any one of Claims 1-19 or pharmacologically acceptable salts thereof.

22. A therapeutic and/or preventive agnet of diabetes mellitus containing as effective ingredient a compound in accordance with any one of Claims 1-20 or pharmacologically acceptable salts thereof.

23. A therapeutic and/or preventive agnet of obesity containing as effective ingredient a compound in accordance with any one of Claims 1-20 or pharmacologically acceptable salts thereof.

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